



INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(51) International Patent Classification ⁶ : A31K 31/495, 31/44, C07D 403/00, 401/00, 241/02, 451/00	A1	(11) International Publication Number: WO 95/25443 (43) International Publication Date: 28 September 1995 (28.09.95)
(21) International Application Number: PCT/US95/03738 (22) International Filing Date: 23 March 1995 (23.03.95) (30) Priority Data: 217,270 24 March 1994 (24.03.94) US (60) Parent Application or Grant (63) Related by Continuation US 217,270 (CIP) Filed on 24 March 1994 (24.03.94) (71) Applicant (for all designated States except US): MERCK & CO., INC. [US/US]; 126 East Lincoln Avenue, Rahway, NJ 07065 (US). (72) Inventors; and (75) Inventors/Applicants (for US only): BOCK, Mark, G. [US/US]; 126 East Lincoln Avenue, Rahway, NJ 07065 (US). EVANS, Ben, E. [US/US]; 126 East Lincoln Avenue, Rahway, NJ 07065 (US). CULBERSON, J., Christopher [US/US]; 126 East Lincoln Avenue, Rahway, NJ 07065 (US). GILBERT, Kevin, F. [US/US]; 126 East Lincoln Avenue, Rahway, NJ 07065 (US). RITTLE, Kenneth, E. [US/US]; 126 East Lincoln Avenue, Rahway, NJ 07065 (US).	(US). WILLIAMS, Peter, D. [US/US]; 126 East Lincoln Avenue, Rahway, NJ 07065 (US). (74) Common Representative: MERCK & CO., INC.; Patent Dept., 126 East Lincoln Avenue, Rahway, NJ 07065 (US). (81) Designated States: AM, AU, BB, BG, BR, BY, CA, CN, CZ, EE, FI, GE, HU, IS, JP, KG, KR, KZ, LK, LR, LT, LV, MD, MG, MN, MX, NO, NZ, PL, RO, RU, SG, SI, SK, TJ, TT, UA, US, UZ, European patent (AT, BE, CH, DE, DK, ES, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, ML, MR, NE, SN, TD, TG), ARIPO patent (KE, MW, SD, SZ, UG). Published <i>With international search report.</i> <i>Before the expiration of the time limit for amending the claims and to be republished in the event of the receipt of amendments.</i>	
(54) Title: TOCOLYTIC OXYTOCIN RECEPTOR ANTAGONISTS (57) Abstract <p>Compounds of the formula X-Y-R, or the pharmaceutically acceptable salts and esters thereof, wherein X, Y and R are defined as in the specification. Such compounds are useful as oxytocin and vasopressin receptor antagonists.</p>		

BEST AVAILABLE COPY

FOR THE PURPOSES OF INFORMATION ONLY

Codes used to identify States party to the PCT on the front pages of pamphlets publishing international applications under the PCT.

AT	Austria	GB	United Kingdom	MR	Mauritania
AU	Australia	GE	Georgia	MW	Malawi
BB	Barbados	GN	Guinea	NE	Niger
BE	Belgium	GR	Greece	NL	Netherlands
BF	Burkina Faso	HU	Hungary	NO	Norway
BG	Bulgaria	IE	Ireland	NZ	New Zealand
BJ	Benin	IT	Italy	PL	Poland
BR	Brazil	JP	Japan	PT	Portugal
BY	Belarus	KE	Kenya	RO	Romania
CA	Canada	KG	Kyrgyzstan	RU	Russian Federation
CF	Central African Republic	KP	Democratic People's Republic of Korea	SD	Sudan
CG	Congo	KR	Republic of Korea	SE	Sweden
CH	Switzerland	KZ	Kazakhstan	SI	Slovenia
CI	Côte d'Ivoire	LI	Liechtenstein	SK	Slovakia
CM	Cameroon	LK	Sri Lanka	SN	Senegal
CN	China	LU	Luxembourg	TD	Chad
CS	Czechoslovakia	LV	Latvia	TG	Togo
CZ	Czech Republic	MC	Monaco	TJ	Tajikistan
DE	Germany	MD	Republic of Moldova	TT	Trinidad and Tobago
DK	Denmark	MG	Madagascar	UA	Ukraine
ES	Spain	ML	Mali	US	United States of America
FI	Finland	MN	Mongolia	UZ	Uzbekistan
FR	France			VN	Viet Nam
GA	Gabon				

- 1 -

TITLE OF THE INVENTION

TOCOLYTIC OXYTOCIN RECEPTOR ANTAGONISTS

FIELD OF THE INVENTION

5 This application is a continuation-in-part of U.S. Serial No. 08/217,270, filed March 24, 1994, the contents of which are hereby incorporated by reference.

10 The present invention provides novel compounds, novel compositions, methods of their use and methods of their manufacture, such compounds are generally pharmacologically useful as agents in obstetric and gynecologic therapy. The aforementioned pharmacologic activities are useful in the treatment of mammals. More specifically, the compounds of the present invention can be used in the treatment of preterm labor, stopping labor preparatory to Caesarean delivery, and in
15 the treatment of dysmenorrhea. At the present time, there is a need in the area of obstetric and gynecologic therapy for such agents.

BACKGROUND OF THE INVENTION

20 In the field of obstetrics, one of the most important problems is the management of preterm labor. A significant number of the pregnancies progressing past 20 weeks of gestation experience premature labor and delivery, which is a leading cause of neonatal morbidity and mortality. Despite major advances in neonatal care, retention of the fetus *in utero* is preferred in most instances.

25 Tocolytic (uterine-relaxing) agents that are currently in use include β_2 -adrenergic agonists, magnesium sulfate and ethanol. Ritodrine, the leading β_2 -adrenergic agonist, causes a number of cardiovascular and metabolic side effects in the mother, including tachycardia, increased renin secretion, hyperglycemia (and reactive
30 hypoglycemia in the infant). Other β_2 -adrenergic agonists, including terbutaline and albuterol have side effects similar to those of ritodrine. Magnesium sulfate at plasma concentrations above the therapeutic range of 4 to 8 mg/dL can cause inhibition of cardiac conduction and neuromuscular transmission, respiratory depression and cardiac arrest,

- 2 -

thus making this agent unsuitable when renal function is impaired. Ethanol is as effective as ritodrine in preventing premature labor, but it does not produce a corresponding reduction in the incidence of fetal respiratory distress that administration of ritodrine does.

5 It has been proposed that a selective oxytocin antagonist would be the ideal tocolytic agent. In the last few years, evidence has accumulated to strongly suggest that the hormone oxytocin may be a physiological initiator of labor in several mammalian species including humans. Oxytocin is believed to exert this effect in part by directly
10 contracting the uterine myometrium and in part by enhancing the synthesis and release of contractile prostaglandins from the uterine endometrium/decidua. These prostaglandins may, in addition, be important in the cervical ripening process. By these mechanisms, the process of labor (term and preterm) is initiated by a heightened
15 sensitivity of the uterus to oxytocin, resulting in part as a result of a well-documented increase in the number of oxytocin receptors in this tissue. This "up-regulation" of oxytocin receptors and enhanced uterine sensitivity appears to be due to trophic effects of rising plasma levels of estrogen towards term. By blocking oxytocin, one would block both the
20 direct (contractile) and indirect (enhanced prostaglandin synthesis) effects of oxytocin on the uterus. A selective oxytocin blocker, or antagonist, would likely be more efficacious for treating preterm labor than current regimens. In addition, since oxytocin at term has major effects only on the uterus, such an oxytocin antagonizing compound
25 would be expected to have few, if any, side effects.

The compounds of the present invention can also be useful in the treatment of dysmenorrhea. This condition is characterized by cyclic pain associated with menses during ovulatory cycles. The pain is
30 thought to result from uterine contractions and ischemia, probably mediated by the effect of prostaglandins produced in the secretory endometrium. By blocking both the direct and indirect effects of oxytocin on the uterus, a selective oxytocin antagonist can be more efficacious for treating dysmenorrhea than current regimens. An

- 3 -

additional use for the present invention is for the stoppage of labor preparatory to Caesarean delivery.

It is, therefore, a purpose of this invention to provide substances which more effectively antagonize the function of oxytocin in disease states in animals, preferably mammals, especially in humans. It is another purpose of this invention to prepare novel compounds which more selectively inhibit oxytocin. It is still another purpose of this invention to provide a method of antagonizing the functions of oxytocin in disease states in mammals. It is also a purpose of this invention to develop a method of preventing or treating oxytocin-related disorders of preterm labor and dysmenorrhea by antagonizing oxytocin.

It has now been found that compounds of the present invention are antagonists of oxytocin and bind to the oxytocin receptor. When the oxytocin receptor is bound by the compounds of the present invention, oxytocin is antagonized by being blocked from its receptor and thus being unable to exert its biologic or pharmacologic effects. These compounds are useful in the treatment and prevention of oxytocin-related disorders of animals, preferably mammals and especially humans. These disorders are primarily preterm labor and dysmenorrhea. The compounds would also find usefulness for stoppage of labor preparatory to Caesarean delivery. Additionally, such compounds are useful in inducing contraception in mammals inasmuch as oxytocin antagonists have now been shown to inhibit the release of oxytocin-stimulated luteinizing hormone (LH) by anterior pituitary cells.

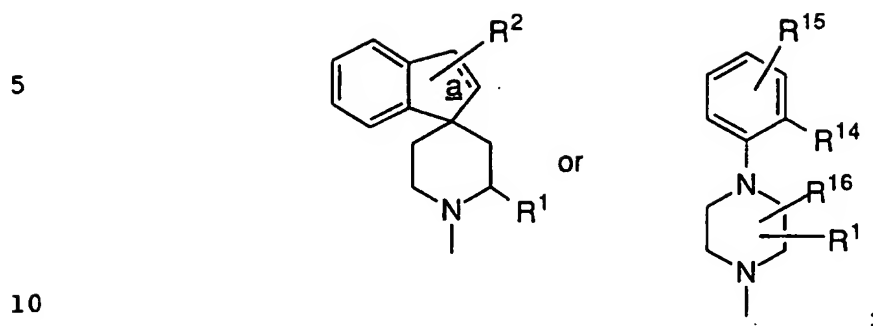
Compounds of the present invention are also inhibitors of vasopressin and can bind to the vasopressin receptor. These compounds are useful in inducing vasodilation, treating hypertension, inducing diuresis and inhibiting platelet agglutination.

SUMMARY OF THE INVENTION

The compounds and their pharmaceutically acceptable salts and esters of the present invention are of the general formula X-Y-R, wherein

- 4 -

X is

a is a single or double bond;

15 Y is selected from the group consisting of -COO-, -CONR²-,
-C(=NR²)-, -SO₂-, -CO-(CH₂)_n-, -(CH₂)_p- and -(CH₂)_p-CO-;

20 R is selected from the group consisting of furyl, thienyl, pyrrolyl,
naphthyl, indolyl, benzimidazolyl, tetrahydronaphthyl, pyridyl, quinolyl,
unsubstituted or substituted cyclohexyl where said substituent is R⁴, and
unsubstituted or substituted phenyl where said substituents are one or
more of R⁵, R⁶ or R⁷;

25 R¹ is selected from the group consisting of hydrogen, C₁₋₅ alkyl,
cyano, carboxyl, phenyl, -CONHR², -CONR²R², -CO₂R³, -COR³,
-(CH₂)_m-OR², -(CH₂)_p-S(O)_r-R², -(CH₂)_m-CO₂R², -(CH₂)_m-N₃,
-(CH₂)_m-NH₂ and -(CH₂)_m-NR²R²;

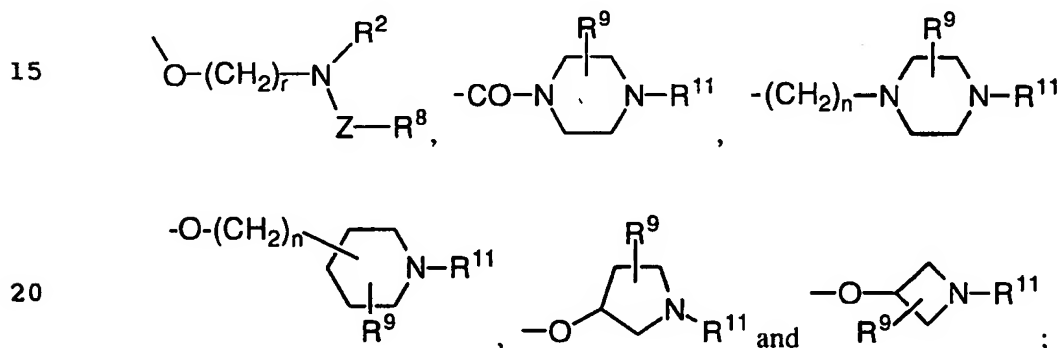
30 R² is selected from the group consisting of hydrogen, benzyl,
C₃₋₈ cycloalkyl and C₁₋₅ alkyl;

R³ is selected from the group consisting of C₁₋₅ alkyl and phenyl;R⁴ is selected from the group consisting of hydrogen, oxo, hydroxyl,
C₁₋₅ alkyl and C₁₋₅ alkoxy;

- 5 -

R⁵ and R⁶ are each independently selected from the group consisting of hydrogen, C₁₋₅ alkyl, C₁₋₅ alkoxy, trifluoromethoxy, 2,2,2-trifluoroethoxy, allyloxy, propargyloxy, trifluoromethyl, C₃₋₈ cycloalkyloxy, cyclopropylmethoxy, hydroxy, hydroxyalkyl, cyano, nitro, amino, halogen, $-(CH_2)_n-CO-R^{10}$, $-O(CH_2)_n-CO-R^{10}$, $-(CH_2)_n-R^{10}$, $-OCH_2(CH_2)_q-R^{10}$, $-OCH_2(CH_2)_q-N(R^2)-R^{17}$ and $-(CH_2)_n-N(R^2)-R^{17}$;

R⁷ is selected from the group consisting of hydrogen, C₁₋₅ alkyl, halogenated C₁₋₅ alkyl, phenyl, phenyl C₁₋₅ alkyl, amino C₂₋₅ alkoxy, C₁₋₅ alkoxy, carboxyl, carboxy C₁₋₅ alkyl, C₁₋₅ alkoxycarbonyl, halogen, hydroxyl,



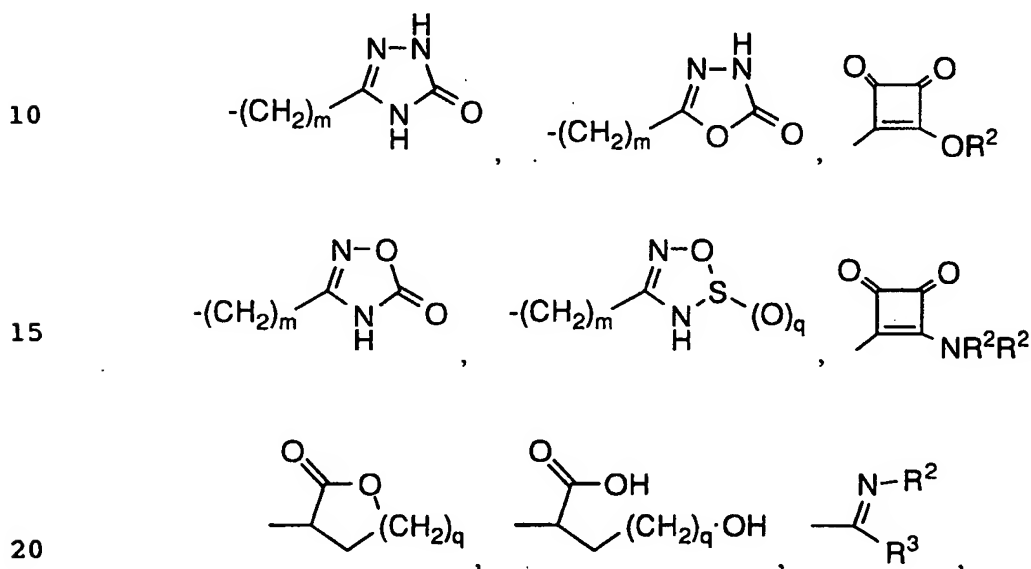
R⁸ is selected from the group consisting of hydrogen, Het, C₁₋₅ alkoxy, unsubstituted C₁₋₅ alkyl and substituted C₁₋₅ alkyl where said substituent is selected from the group consisting of carboxyl, hydroxyl, amino, $-N(R^2)_2$, $-NHR^2$, C₁₋₁₀ alkoxycarbonylamino and Het;

R⁹ is selected from the group consisting of hydrogen, C₁₋₅ alkyl, hydroxyalkyl, methylthioalkyl, methylsulfonylalkyl, methylsulfonyl, cyano, carbamoyl, $-(CH_2)_n-CO_2H$, $-(CH_2)_p-R^{10}$ and $-(CH_2)_p-COR^{10}$;

R¹⁰ is selected from the group consisting of hydroxyl, C₁₋₅ alkoxy, amino, $-N(R^2)_2$, $-NHR^2$, 1-piperazinyl, 4-methyl-1-piperazinyl, pyridinyl, 4-morpholinyl, 1-pyrrolidinyl and 1-piperidinyl;

- 6 -

R¹¹ is selected from the group consisting of hydrogen,
 C₁₋₅ alkoxy carbonyl, C₁₋₅ alkyl carbonyl, C₁₋₅ alkyl, allyl,
 5 5-tetrazolyl, 2-pyrimidinyl, 2-pyrazinyl, 2-pyridyl, 4-pyridyl,
 4-piperidinyl, 1-methyl-4-piperidinyl, 4-tetrahydropyranyl,
 -CO-NH-COR¹², -CO-NH-SO₂R¹², -SO₂-NH-COR¹², -Z-R¹³,



and substituted C₁₋₁₀ alkyl wherein said substituent on said alkyl is
 selected from the group consisting of hydroxyl, C₁₋₁₀ alkoxy,
 C₁₋₁₀ alkoxy carbonyl, carboxyl, -SO₂NH₂, amino, -N(R²)₂, -NHR²,
 25 1-piperazinyl, 4-methyl-1-piperazinyl, pyridinyl, quinolinyl,
 4-morpholinyl, 1-pyrrolidinyl, imidazolyl, 4-piperidinyl, 1-methyl-4-
 piperidinyl, 1-piperidinyl, 5-tetrazolyl, unsubstituted, mono-, di- or tri-
 substituted pyridyl wherein said substituents on said pyridyl are
 independently selected from halogen, C₁₋₅ alkoxy, alkylenedioxy,
 30 C₁₋₅ alkyl, C₁₋₁₀ alkoxy carbonyl, carboxyl, trifluoromethyl, -SO₂CH₃
 or -SO₂NH₂, and unsubstituted, mono-, di- or tri-substituted phenyl
 wherein said substituents on said phenyl are independently selected from
 the group consisting of halogen, C₁₋₅ alkoxy, alkylenedioxy,
 C₁₋₅ alkyl, C₁₋₁₀ alkoxy carbonyl, carboxyl, trifluoromethyl,
 -SO₂CH₃, and -SO₂NH₂;

- 7 -

5 R¹² is selected from the group consisting of C₁₋₁₀ alkyl, trifluoromethyl, and phenyl optionally substituted with one to three members of the group consisting of C₁₋₅ alkyl, C₁₋₁₀ alkoxy, halogen and trifluoromethyl;

10 R¹³ is selected from the group consisting of C₁₋₁₀ alkyl, C₁₋₁₀ alkoxy, amino, carboxyl, phenyl, vinyl, morpholinyl, piperidinyl, pyrrolidinyl, pyridinyl, piperazinyl, 1-methyl-4-piperazinyl, 1-alkoxy-carbonyl-4-piperidinyl, -N(R²)-(CH₂)_i-R¹⁰, substituted phenyl wherein the substituent is selected from the group consisting of nitro, C₁₋₁₀ alkoxy, amino, monoalkylamino, dialkylamino, halogen, 1-piperazinyl, 4-piperidinyloxy, 4-methyl-1-piperazinyl, C₁₋₁₀ alkoxycarbonyl, carboxyl, amino C₁₋₁₀ alkyl, 15 monoalkylaminoalkyl, dialkylaminoalkyl, 4-morpholinylalkyl, 1-piperazinylalkyl, and 4-methyl-1-piperazinylalkyl; and substituted C₁₋₁₀ alkyl wherein the substituent is selected from the group consisting of phenyl, hydroxyl, C₁₋₁₀ alkoxy, C₁₋₁₀ alkoxycarbonyl, carboxyl, halogen, amino, -N(R²)₂, -NHR², 1-piperazinyl, 1-methyl-4-piperazinyl, pyridinyl, 4-morpholinyl, pyrrolidinyl, imidazolyl, 20 5-tetrazolyl, azetidyl, piperidinyl, and substituted phenyl wherein the substituent is selected from the group consisting of nitro, C₁₋₁₀ alkoxy, amino, monoalkylamino, dialkylamino, halogen, 1-piperazinyl, 4-piperidinyloxy, 4-methyl-1-piperazinyl, C₁₋₁₀ alkoxycarbonyl, 25 carboxyl, aminoalkyl, monoalkylaminoalkyl, dialkylaminoalkyl, 4-morpholinylalkyl, 1-piperazinylalkyl, and 4-methyl-1-piperazinylalkyl;

30 R¹⁴ and R¹⁵ are each independently selected from the group consisting of hydrogen, C₁₋₅ alkyl, C₁₋₅ alkoxy, halogen, nitro and cyano;

R¹⁶ is selected from the group consisting of hydrogen and oxo;

R¹⁷ is selected from the group consisting of hydrogen, R² and -Z-R¹⁸;

- 8 -

R¹⁸ is selected from the group consisting of C₁₋₅ alkoxyl, Het,
 unsubstituted or substituted C₁₋₅ alkyl where said substituent is Het and
 unsubstituted or substituted C₂₋₅ alkenyl where said substituent is Het;

5

Het is selected from the group consisting of imidazolyl, piperidinyl,
 C₁₋₅ alkyl-substituted piperidinyl, piperazinyl, C₁₋₅ alkyl-substituted
 piperazinyl, benzimidazolyl, carboxymethyl-substituted benzimidazolyl,
 indolyl, morpholinyl, tetrazolyl, C₁₋₅ alkylcarbonyl-substituted
 piperidinyl, C₁₋₅ alkoxy carbonyl-substituted piperidinyl, pyrrolidinyl,
 C₁₋₅ alkyl-substituted pyrrolidinyl, and pyridinyl;

10

Z is -CO- or -SO₂-;

15

i is an integer of from 2 to 5;

m is an integer of from 1 to 5;

20

n is an integer of from 0 to 3;

p is an integer of from 1 to 3; and

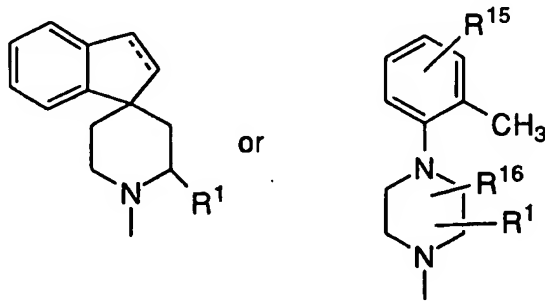
q is an integer of from 1 to 2;

25

r is an integer of from 0 to 2;

provided that when X is

30



- 9 -

and Y is $-\text{SO}_2-$, $-\text{CO}-(\text{CH}_2)_n-$ or $-(\text{CH}_2)_p-$; and

R^{15} is hydrogen, methyl or halogen; and

R is thienyl, naphthyl, indolyl, pyridyl, quinolyl, unsubstituted or substituted cyclohexyl where said substituent is R^4 , or unsubstituted or substituted phenyl where said substituents are one or more of R^5 , R^6 or R^7 ; then R^1 is not hydrogen.

In one embodiment of the instant invention are the compounds wherein

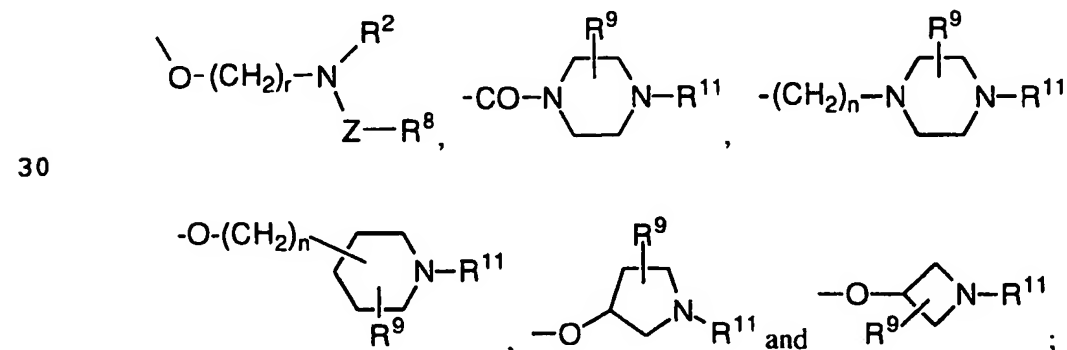
Y is selected from the group consisting of $-\text{SO}_2-$, $-\text{CO}-(\text{CH}_2)_n-$ and $-(\text{CH}_2)_p-$;

R is unsubstituted or substituted phenyl where said substituents are one or more of R^5 , R^6 or R^7 ;

R^1 is selected from the group consisting of hydrogen, cyano, phenyl, $-\text{CONHR}^2$, $-\text{CONR}^2\text{R}^2$, $-(\text{CH}_2)_m-\text{OR}^2$, $-(\text{CH}_2)_p-\text{S}(\text{O})_r-\text{R}^2$, $-(\text{CH}_2)_m-\text{CO}_2\text{R}^2$, $-(\text{CH}_2)_m-\text{N}_3$, $-(\text{CH}_2)_m-\text{NH}_2$ and $-(\text{CH}_2)_m-\text{NR}^2\text{R}^2$;

R^5 and R^6 are each independently selected from the group consisting of hydrogen, C1-5 alkyl, C1-5 alkoxy, halogen, $-(\text{CH}_2)_n-\text{CO}-\text{R}^{10}$, $-\text{O}(\text{CH}_2)_n-\text{CO}-\text{R}^{10}$, $-(\text{CH}_2)_n-\text{R}^{10}$, $-\text{OCH}_2(\text{CH}_2)_q-\text{R}^{10}$, $-\text{OCH}_2(\text{CH}_2)_q-\text{N}(\text{R}^2)-\text{R}^{17}$ and $-(\text{CH}_2)_n-\text{N}(\text{R}^2)-\text{R}^{17}$;

R^7 is selected from the group consisting of hydrogen,



- 10 -

R⁹ is hydrogen;

R¹⁴ is selected from the group consisting of C₁₋₅ alkyl, C₁₋₅ alkoxy and halogen; and

5

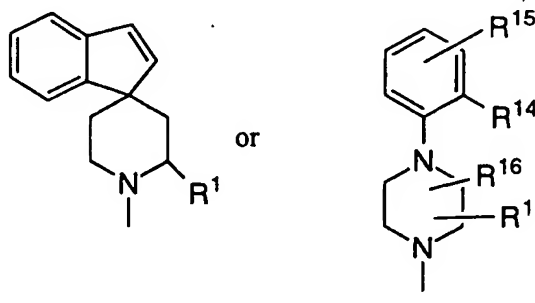
R¹⁵ is selected from the group consisting of hydrogen and C₁₋₅ alkyl.

In one class of this embodiment are the compounds wherein

X is

10

15



Y is selected from the group consisting of -(CH₂)_p- and -CO-(CH₂)_n-;

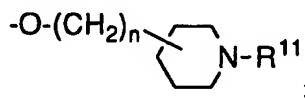
20

R² is selected from the group consisting of hydrogen, C₃₋₈ cycloalkyl and C₁₋₅ alkyl;

R⁵ and R⁶ are each independently selected from the group consisting of hydrogen, C₁₋₅ alkoxy, halogen and -(CH₂)_n-N(R²)-R¹⁷;

25

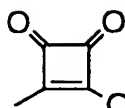
R⁷ is selected from the group consisting of hydrogen and



30

R¹¹ is selected from the group consisting of hydrogen,

- 11 -



C₁₋₅ alkylcarbonyl, -Z-R¹³, and substituted C₁₋₅ alkyl
 wherein said substituent on said alkyl is unsubstituted, mono-, di- or tri-
 5 substituted pyridyl wherein said substituents on said pyridyl are
 independently selected from the group consisting of halogen, C₁₋₅ alkyl
 and C₁₋₅ alkoxy;

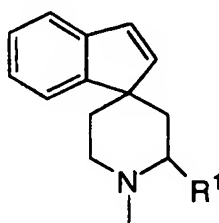
R¹³ is selected from the group consisting of unsubstituted C₁₋₁₀ alkyl
 10 and substituted C₁₋₁₀ alkyl wherein said substituent is selected from the
 group consisting of -N(R²)₂, -NHR² and imidazolyl;

R¹⁷ is -Z-R¹⁸; and

15 Het is selected from the group consisting of imidazolyl, benzimidazolyl,
 carboxymethyl-substituted benzimidazolyl and indolyl.

In one subclass are the compounds wherein

20 X is



25

R¹ is selected from the group consisting of hydrogen, phenyl, cyano and
 -CONHR²;

30 R⁵ is -NH-CO-R¹⁸;

R⁶ and R⁷ are hydrogen; and

R¹⁸ is selected from Het or substituted C₂₋₅ alkenyl wherein said
 substituent is Het.

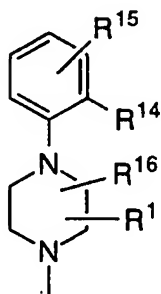
- 12 -

In a second subclass are the compounds wherein

X is

5

10



; and

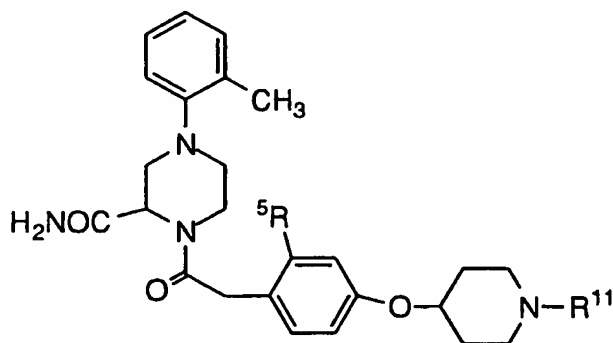
15

R¹ is selected from the group consisting of hydrogen, -CONHR², -(CH₂)_m-CO₂R², -(CH₂)_m-OR², -(CH₂)_p-S(O)_rR², -(CH₂)_m-N₃, -(CH₂)_m-NH₂ and -(CH₂)_m-NR²₂.

Illustrative of this second subclass are the compounds of the structure

20

25



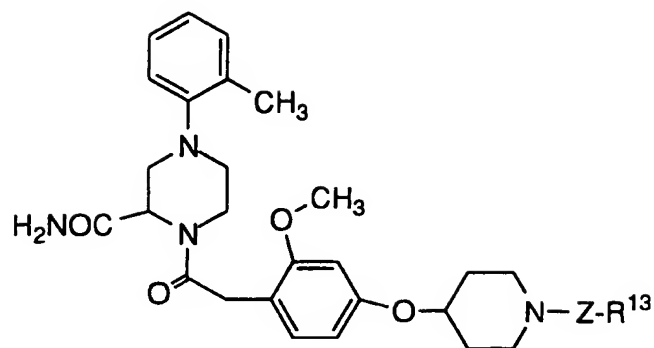
wherein R⁵ is C₁-5 alkoxy.

Further illustrating this subclass are the compounds of the structure

30

- 13 -

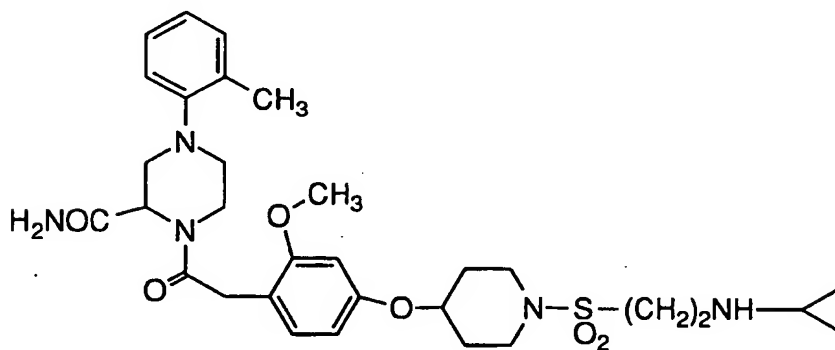
5



10

Exemplifying this subclass is the compound of the structure

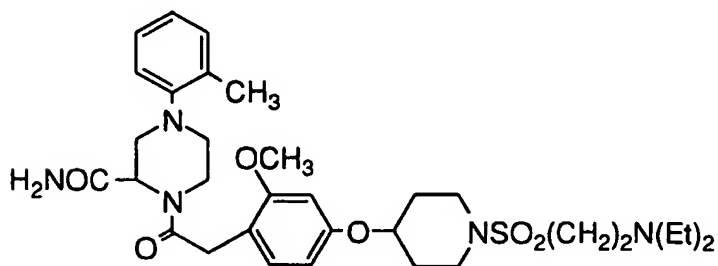
15



20

An example of this subclass is the compound of the structure

25



30

Further illustrating the instant invention is a pharmaceutical composition comprising a pharmaceutically acceptable carrier and a pharmacologically effective amount of a compound of the instant invention to prevent preterm labor in a mammal in need thereof.

- 14 -

Another illustration of the invention is a method of eliciting an oxytocin antagonizing effect in a mammal, comprising the step of administering to the mammal a pharmacologically effective amount of a compound of the instant invention.

5 Specific illustrations of the instant invention are methods of treating preterm labor, stopping labor preparatory to cesarian delivery and treating dysmenorrhea in a mammal in need thereof, comprising the step of administering to the mammal a pharmacologically effective amount of a compound of the instant invention.

10 Further exemplifying the invention is a method of antagonizing vasopressin from binding to its receptor site in a mammal, comprising the step of administering to said mammal a pharmacologically effective amount of a compound of the instant invention.

15 Specific examples of the instant invention are methods of inducing vasodilation, treating hypertension, inducing diuresis and inhibiting platelet agglutination in a mammal in need thereof, comprising the step of administering to said mammal a pharmacologically effective amount of a compound of the instant invention.

20 Another example of the instant invention is a method of causing contraception in a mammal in need thereof, comprising the step of administering to said mammal a pharmacologically effective amount of a compound of the instant invention.

25 More particularly illustrating the invention are methods of increasing fertility and embryonic survival in a farm animal and controlling the timing of estrus in a farm animal, comprising administering to the farm animal a pharmacologically effective amount of any of the compounds of the present invention. An additional illustration of the present invention is a method for improving survival of a farm animal neonate comprising controlling timing of parturition to effect delivery of the neonate during daylight hours by administering to a farm animal which is expected to deliver the neonate within 24

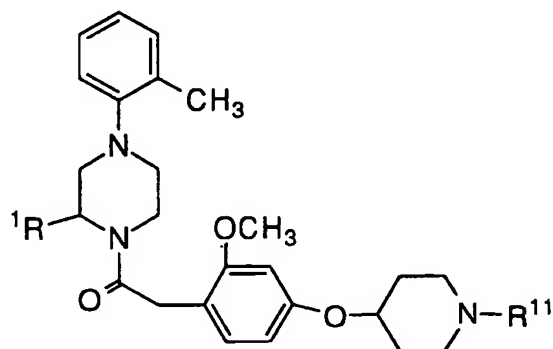
- 15 -

hours a pharmacologically effective amount of any of the compounds of the present invention.

More particularly exemplifying the invention is a compound of the formula

5

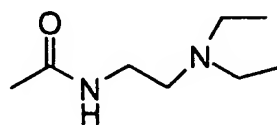
10



15 wherein

20

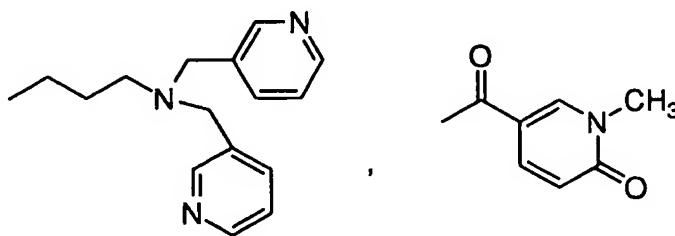
R¹ is selected from -CONH₂ and



; and

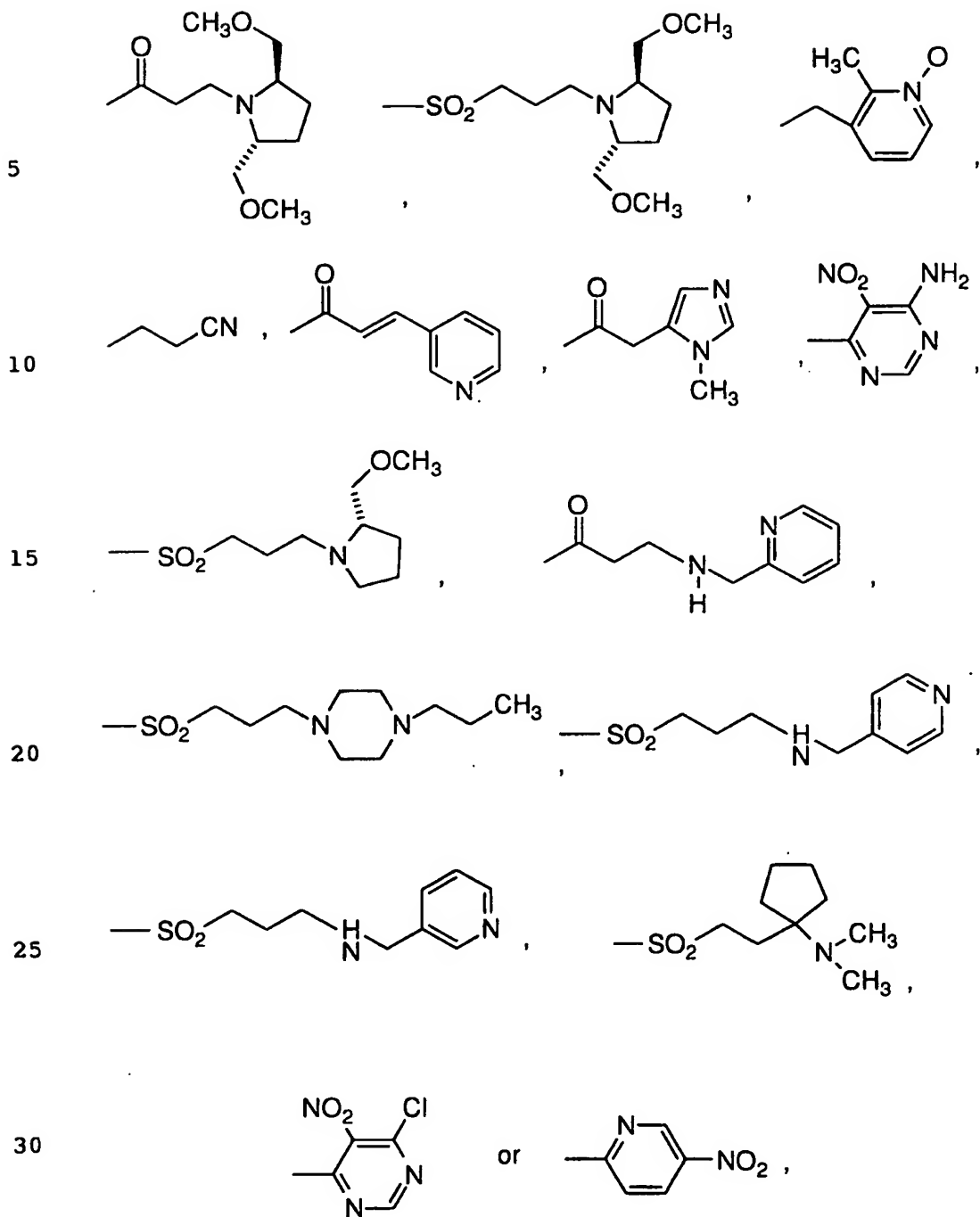
R¹¹ is selected from C₁-5 alkylcarbonyl, C₁-5 alkoxy carbonyl,

25



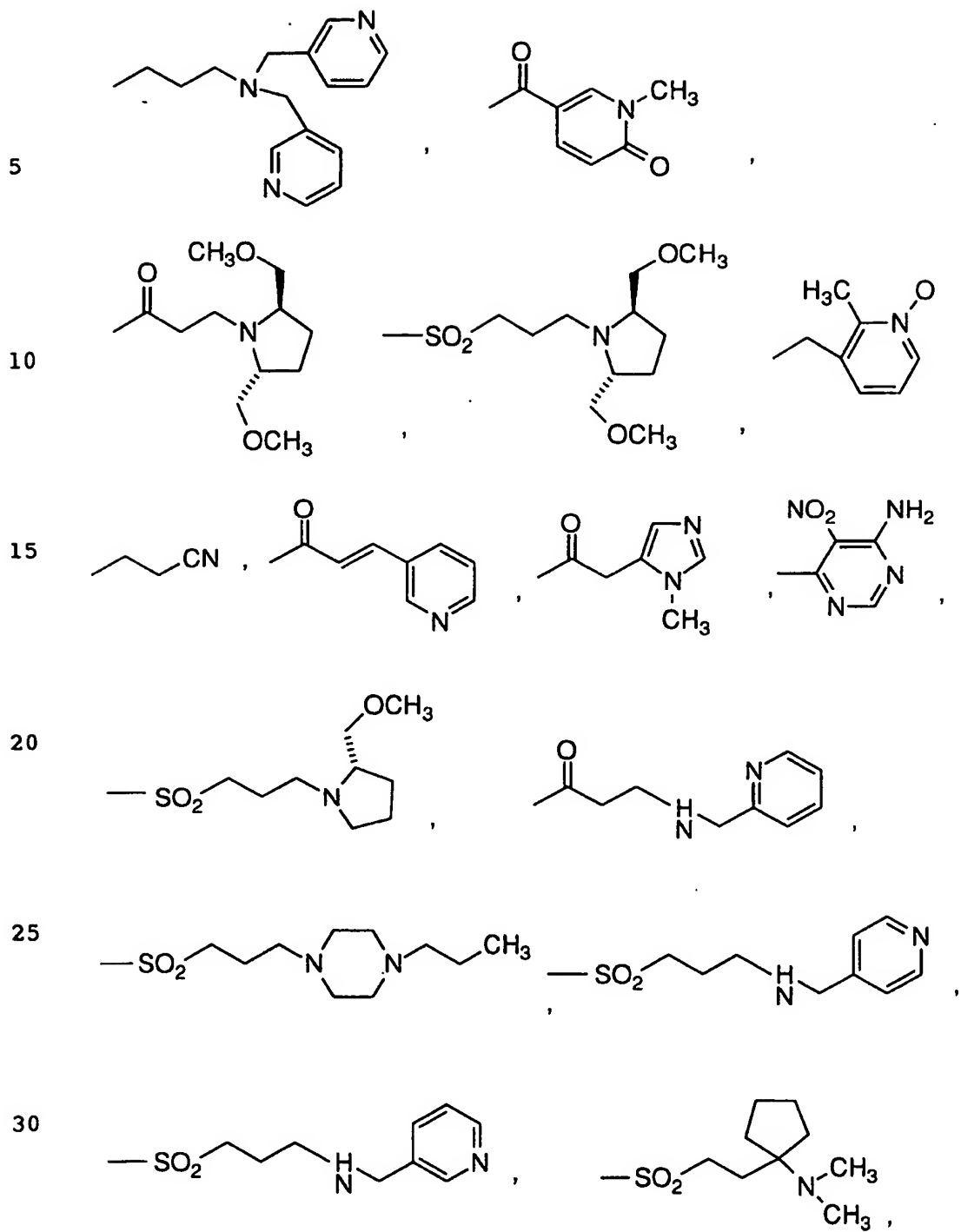
30

- 16 -

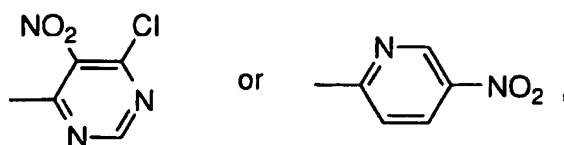


and the pharmaceutically acceptable salts thereof. Preferably, R¹ is -CONH₂; and R¹¹ is selected from

- 17 -



- 18 -



5 Additional examples of the invention are the use of any of the compounds described above in the preparation of a medicament for the treatment of: preterm labor, dysmenorrhea and stopping labor prior to cesarean delivery.

10 Salts encompassed within the term "pharmaceutically acceptable salts and esters" refer to non-toxic salts of the compounds of this invention which are generally prepared by reacting the free base with a suitable organic or inorganic acid. Representative salts include the following:

15 Acetate, Benzenesulfonate, Benzoate, Bicarbonate, Bisulfate, Bitartrate, Borate, Bromide, Calcium, Camsylate, Carbonate, Chloride, Clavulanate, Citrate, Dihydrochloride, Edetate, Edisylate, Estolate, Esylate, Fumarate, Gluceptate, Gluconate, Glutamate, Glycollylarsanilate, Hexylresorcinate, Hydrabamine, Hydrobromide, Hydrochloride, Hydroxynaphthoate, Iodide, Isothionate, Lactate, 20 Lactobionate, Laurate, Malate, Maleate, Mandelate, Mesylate, Methylbromide, Methylnitrate, Methylsulfate, Mucate, Napsylate, Nitrate, N-methylglucamine ammonium salt, Oleate, Oxalate, Pamoate (Embonate), Palmitate, Pantothenate, Phosphate/diphosphate, Polygalacturonate, Salicylate, Stearate, Sulfate, Subacetate, Succinate, 25 Tannate, Tartrate, Teoclate, Tosylate, Triethiodide and Valerate.

Esters encompassed within the term "pharmaceutically acceptable salts and esters" refer to non-toxic esters, preferably the alkyl esters such as methyl, ethyl, propyl, isopropyl, butyl, isobutyl or pentyl esters, of which the methyl ester is preferred. However, other 30 esters such as phenyl-C₁₋₅ alkyl may be employed if desired.

Where the compounds of the instant invention contain a carboxylic acid moiety, esters, preferably alkyl esters, of the carboxylic acids may be obtained by contacting the carboxylic acid with an appropriate alcohol, preferably in the presence of an acid catalyst, for

- 19 -

example, a mineral acid (such as hydrochloric acid or sulfuric acid), a Lewis acid (e.g., boron trifluoride) or an acidic ion exchange resin. The solvent employed for this reaction is not critical, provided that it does not adversely affect the reaction; suitable solvents include the alcohol itself, benzene, chloroform, ether and the like. Alternatively, esters may be obtained by contacting the carboxylic acid with a diazoalkane, in which the alkane moiety may be substituted or unsubstituted. This reaction is usually effected by contacting the acid with an ethereal solution of the diazoalkane. As a further alternative, the ester may be obtained by contacting a metal salt of the carboxylic acid with a halide, preferably an alkyl halide, in a suitable solvent; preferred solvents include dimethylformamide, tetrahydrofuran, dimethylsulfoxide and acetone.

Also included within the scope of the invention are polymorphs and hydrates of the compounds of the instant invention. In addition, where a compound is chiral, the separate enantiomers, substantially free of the other, are also included within the scope of the invention; further included are all mixtures of the two enantiomers.

The term "pharmacologically effective amount" shall mean that amount of a drug or pharmaceutical agent that will elicit the biological or medical response of a tissue, system, animal or human that is being sought by a researcher or clinician.

The term "alkyl" shall mean straight or branched chain alkanes of one to ten total carbon atoms, or any number within this range (i.e., methyl, ethyl, 1-propyl, 2-propyl, n-butyl, t-butyl, etc.).

The term "alkenyl" shall mean straight or branched chain alkenes with one or more degrees of unsaturation at any position on the chain, of two to ten total carbon atoms, or any number within this range.

The term "alkynyl" shall mean straight or branched chain alkynes with one or more degrees of unsaturation at any position on the chain, of two to ten total carbon atoms, or any number within this range.

The term "aryl" shall mean phenyl, naphthyl or fluorenyl.

- 20 -

The term "cycloalkyl" shall mean cyclic rings of alkanes of three to eight total carbon atoms (i.e., cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl or cyclooctyl).

5 Whenever the term "alkyl" or "aryl" or either of their prefix roots appear in a name of a substituent (e.g., aralkoxyaryloxy) it shall be interpreted as including those limitations given above for "alkyl" and "aryl." Designated numbers of carbon atoms (e.g., C₁₋₁₀) shall refer independently to the number of carbon atoms in an alkyl or cyclic alkyl moiety or to the alkyl portion of a larger substituent in
10 which alkyl appears as its prefix root.

The term "halogen" shall include iodine, bromine, chlorine and fluorine.

The term "preterm labor" shall mean expulsion from the uterus of a viable infant before the normal end of gestation, or more
15 particularly, onset of labor with effacement and dilation of the cervix before the 37th week of gestation. It may or may not be associated with vaginal bleeding or rupture of the membranes.

The term "dysmenorrhea" shall mean painful menstruation.

20 The term "Caesarean delivery" shall mean incision through the abdominal and uterine walls for delivery of a fetus.

The term "substituted" shall be deemed to include multiple degrees of substitution by a named substituent.

25 Where multiple substituent moieties are disclosed or claimed, the substituted compound can be independently substituted by one or more of the disclosed or claimed substituent moieties, singly or plurally.

30 The ability of the compounds of the present invention to antagonize oxytocin makes these compounds useful as pharmacologic agents for mammals, especially for humans, for the treatment and prevention of disorders wherein oxytocin may be involved. Examples of such disorders include preterm labor and especially dysmenorrhea. These compounds may also find usefulness for stoppage of labor preparatory to Cesarean delivery.

- 21 -

The present invention is also directed to combinations of the compounds of the present invention with one or more agents useful in the treatment of oxytocin related disorders such as preterm labor, dysmenorrhea and stopping labor prior to cesarean delivery. For example, the compounds of the instant invention may be effectively administered in combination with effective amounts of other agents used in the treatment of preterm labor, such as antenatal steroids (e.g., dexamethasone). Preferred combinations are simultaneous or alternating treatments of an oxytocin receptor antagonist of the present invention and an antenatal steroid. These combinations have beneficial effects on the neonate by both decreasing uterine activity to prolong gestation and increasing fetal maturation. In accordance with the method of the present invention, the individual components of the combination can be administered separately at different times during the course of therapy or concurrently in divided or single combination forms. The instant invention is therefore to be understood as embracing all such regimes of simultaneous or alternating treatment and the term "administering" is to be interpreted accordingly. It will be understood that the scope of combinations of the compounds of this invention with other agents useful for treating oxytocin related conditions includes in principle any combination with any pharmaceutical composition useful for treating preterm labor, dysmenorrhea or stopping labor prior to cesarean delivery.

The oxytocin antagonist compounds of the present invention are also useful for improving reproductive efficiency in farm animals. In certain farm animals (e.g., sheep, cattle, swine and goats), the beginning of the estrous cycle is typically marked by behavioral estrus when the female animal accepts the male for mating. Ovulation of the ovarian follicle occurs shortly after onset of estrus and cells in the follicle give rise to the corpus luteum. The cells that form the corpus luteum produce progesterone and they also produce oxytocin. The secretion of oxytocin from the corpus luteum and/or pituitary acts on the uterine endometrium to stimulate the secretion of prostaglandins (in particular PGF) which, in turn, causes the regression of the corpus

- 22 -

luteum of the ovary. PGF is, therefore, the luteolytic hormone. In the cycling animal (i.e., where mating and fertilization have not occurred), destruction of the corpus luteum removes the source of progesterone which is key to the preparation of the uterus for pregnancy. The
5 presence of a viable conceptus (i.e., the embryo and its associated membranes) is necessary to prevent the luteolytic process. In fact, the first key signal that the conceptus must produce is the one to prevent regression of the corpus luteum (i.e., the maternal recognition of pregnancy signal). Thus, in the animal where mating and fertilization
10 have occurred, the conceptus secretes a factor that antagonizes the action of oxytocin to induce luteolysis. This results in maintenance of a functioning corpus luteum and the continued secretion of progesterone which is obligatory to the initiation of pregnancy.

Administration of an oxytocin antagonist of the present
15 invention at this critical period after fertilization (i.e., just prior to or during the period of maternal recognition of pregnancy) supplements the natural signal from the conceptus (i.e., maternal recognition of pregnancy) to prolong corpus luteal function. The result is to increase pregnancy rates by enhancing the chances of impregnation through a
20 reduction in embryonic loss. Thus, to improve fertility in a farm animal, a mated animal, for example, a mated ewe, is treated with an oxytocin antagonist compound beginning on between day 10 to day 15 after onset of estrus. The oxytocin antagonist compound is administered to the mated animal for a period of one day to three weeks, preferably
25 one week to three weeks, most preferably one week to two weeks.

The compounds of the present invention are also useful for controlling the timing of parturition in farm animals so that delivery of the neonates occurs during the daytime. Approximately 80% of livestock are delivered at night and up to 5 to 10% of newborns die
30 because the deliveries are not monitored properly. An oxytocin antagonist compound of the present invention administered to the mother on the evening before expected delivery delays parturition so that the delivery occurs during the daylight hours. By delaying the timing of parturition, proper monitoring of the delivery and the

- 23 -

neonates is ensured, resulting in increased survival rates of the newborns.

5 In addition, the oxytocin antagonists of the instant invention can also be used to control the timing of estrus in a cycling farm animal by preventing luteal regression. An oxytocin antagonist compound of the instant invention is administered to a cycling farm animal prior to expected estrus to prevent regression of the corpus luteum. Daily administration of the compound retards estrus until administration of the compound ceases. Preferably, the oxytocin antagonist compound is
10 administered at least 1 day prior to expected estrus. By delaying estrus in a group of farm animals, a farmer can synchronize estrus among the group to provide time and cost savings in farm management.

The compounds of the present invention also bind to the vasopressin receptor and are therefore useful as vasopressin antagonists.
15 Vasopressin antagonists are useful in the treatment or prevention of disease states involving vasopressin disorders, including their use as diuretics and their use in congestive heart failure.

The compounds of the present invention can be administered in such oral dosage forms as tablets, capsules (each
20 including timed release and sustained release formulations), pills, powders, granules, elixers, tinctures, suspensions, syrups and emulsions. Likewise, they may also be administered in intravenous (both bolus and infusion), intraperitoneal, subcutaneous or intramuscular form, all using forms well known to those of ordinary skill in the pharmaceutical arts.
25 An effective but non-toxic amount of the compound desired can be employed as a tocolytic agent.

The dosage regimen utilizing the compounds of the present invention is selected in accordance with a variety of factors including type, species, age, weight, sex and medical condition of the patient; the
30 severity of the condition to be treated; the route of administration; the renal and hepatic function of the patient; and the particular compound or salt thereof employed. An ordinarily skilled physician or veterinarian can readily determine and prescribe the effective amount of

- 24 -

the drug required to prevent, counter or arrest the progress of the condition.

Oral dosages of the present invention, when used for the indicated effects, will range between about 0.3-6.0 gm/day orally. More particularly, when administered orally for the treatment of preterm labor, an effective daily dose will be in the range of 0.05 mg/kg to about 100 mg/kg of body weight, preferably, from 0.5 mg/kg to 50 mg/kg, administered in single or divided dose. Intravenously, the most preferred doses will range from 0.1 to about 10 mg/minute during a constant rate infusion. Advantageously, compounds of the present invention may be administered in a single daily dose, or the total daily dosage may be administered in divided doses of two, three or four times daily. Furthermore, preferred compounds for the present invention can be administered in intranasal form via topical use of suitable intranasal vehicles, or via transdermal routes, using those forms of transdermal skin patches well known to those of ordinary skill in that art. To be administered in the form of a transdermal delivery system, the dosage administration will, of course, be continuous rather than intermittent throughout the dosage regimen.

In the methods of the present invention, the compounds herein described in detail can form the active ingredient, and are typically administered in admixture with suitable pharmaceutical diluents, excipients or carriers (collectively referred to herein as "carrier" materials) suitably selected with respect to the intended form of administration, that is, oral tablets, capsules, elixirs, syrups and the like, and consistent with conventional pharmaceutical practices.

For instance, for oral administration in the form of a tablet or capsule, the active drug component can be combined with an oral, non-toxic pharmaceutically acceptable inert carrier such as ethanol, glycerol, water and the like. Moreover, when desired or necessary, suitable binders, lubricants, disintegrating agents and coloring agents can also be incorporated into the mixture. Suitable binders include starch, gelatin, natural sugars such as glucose or beta-lactose, corn sweeteners, natural and synthetic gums such as acacia, tragacanth or

- 25 -

5 sodium alginate, carboxymethylcellulose, polyethylene glycol, waxes and the like. Lubricants used in these dosage forms include sodium oleate, sodium stearate, magnesium stearate, sodium benzoate, sodium acetate, sodium chloride and the like. Disintegrators include, without limitation, starch, methyl cellulose, agar, bentonite, xanthan gum and the like.

10 The compounds of the present invention can also be administered in the form of liposome delivery systems, such as small unilamellar vesicles, large unilamellar vesicles and multilamellar vesicles. Liposomes can be formed from a variety of phospholipids, such as cholesterol, stearylamine or phosphatidylcholines.

15 Compounds of the present invention may also be delivered by the use of monoclonal antibodies as individual carriers to which the compound molecules are coupled. The compounds of the present invention may also be coupled with soluble polymers as targetable drug carriers. Such polymers can include polyvinylpyrrolidone, pyran copolymer, polyhydroxypropylmethacrylamide-phenol, polyhydroxyethyl-aspartamidephenol, or polyethyleneoxidepolylysine substituted with palmitoyl residues. Furthermore, the compounds of the present invention may be coupled to a class of biodegradable polymers useful in achieving controlled release of a drug, for example, polylactic acid, polyepsilon caprolactone, polyhydroxy butyric acid, polyorthoesters, polyacetals, polydihydropyrans, polycyanoacrylates and cross-linked or amphipathic block copolymers of hydrogels.

25

Abbreviations used in the Examples are as follows:

30 BOP = benzotriazol-1-yloxytris(dimethylamino)phosphonium
hexafluorophosphate
DIEA = diisopropylethylamine
DMF = dimethylformamide
EtOAc = ethyl acetate
EtOH = ethanol
EDC = 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide

- 26 -

FAB MS = fast atom bombardment mass spectroscopy

HOBT or HBT = 1-hydroxybenzotriazole

HPLC = high pressure liquid chromatography

MeOH = methanol

5 NMR = nuclear magnetic resonance

THF = tetrahydrofuran

TLC = thin layer chromatography

10 All solvents were reagent grade and stored over 4Å molecular sieves. THF was distilled from calcium hydride under inert atmosphere. Dioxane was dried and freed of peroxides by passage through a column of activity I neutral alumina.

Determination of reaction pH was estimated by spotting an aliquot from the reaction mixture on wetted E. Merck pH sticks. ¹H
15 NMR spectra were measured at 300 MHz on a Varian XL-300, at 400 MHz on a Varian XL-400, and at 360 MHz on a Nicolet NT-360 using (CH₃)₄Si as an internal standard. Fast atom bombardment mass spectra (FAB MS) were obtained on a VG-ZAB-HF spectrometer.

Analytical HPLC were run on a Spectra Physics
20 SP4270/8800 instrument using the following conditions:
Column: Vydac C₁₈, 0.21 x 15 cm
Mobile Phases A = 0.1% by volume TFA in H₂O; B = MeOH;
C = 0.1% by volume TFA in acetonitrile
Gradient T = 0 min, 95% A, 5% C
25 T = 15 min, 5% A, 95% C

Flow = 1.5 mL/min

UV detection at 214 nm

Pressurized silica gel column chromatography using 230-
400 mesh silica gel was performed according to the method of Still,
30 Kahn, and Mitra (J. Org. Chem. (1978) vol. 43, p.2923).

The compounds of the present invention can be prepared readily according to the following reaction schemes and examples, or modifications thereof, using readily available starting materials, reagents and conventional synthesis procedures. In these reactions, it is

- 27 -

also possible to make use of variants which are themselves known to those of ordinary skill in this art, but are not mentioned in greater detail.

5 The most preferred compounds of the invention are any or all of those specifically set forth in these Examples. These compounds are not, however, to be construed as forming the only genus that is considered as the invention, and any combination of the compounds or their moieties may itself form a genus. The following examples further illustrate details for the preparation of the compounds of the present
10 invention. Those skilled in the art will readily understand that known variations of the conditions and processes of the following preparative procedures can be used to prepare these compounds. All temperatures are degrees Celsius unless noted otherwise.

15 The compounds and pharmaceutically acceptable salts of the present invention can be synthesized according to the general methods outlined in Schemes 1-3. The spiroindene compounds of the instant invention can be prepared as shown in Scheme 1. Accordingly, spiro[1*H*]indene-1,4'-piperidine I (prepared as described in US
20 4,894,386) is dissolved in an aprotic organic solvent, preferably methylene chloride or N,N-dimethylformamide (DMF) following the usual techniques for the exclusion of moisture. To this solution is then added an acylating agent, such as a carboxylic acid chloride, carboxylic acid anhydride or sulfonic acid chloride, or the like; preferably, a phenylacetic acid analog is added, followed by an amide bond forming
25 agent, for example 1-ethyl-3-(3-dimethylamino-propyl)-carbodiimide hydrochloride (EDC), and an activating agent like 1-hydroxybenzotriazole (HBT). The reaction mixture temperature is maintained between 0°C and 27°C, preferably 23°C, and the pH is monitored throughout the course of the reaction and is adjusted when necessary to
30 approximately 8 with a base like triethylamine (TEA). Extractive workup and purification according to standard procedures affords II.

 Spiro[1*H*]indene-1,4'-piperidine I can also be derivatized in the 2'-position by first forming an intermediate chloramine with a halogenating agent, preferably tert-butylhypochlorite, followed by

- 28 -

elimination of the halide with potassium superoxide in ethyl ether to
give **III**. Imine **III** is then trapped with a suitable alkylmetal or
phenylmetal reagent, for example n-butyllithium or phenyllithium, to
give derivatives like **IV**. Alternatively, functional groups like a nitrile
5 can be introduced with the aid of an agent like trimethylsilylcyanide to
give an aminonitrile which is then further transformed to an amide like
VI according to standard methodology. Both **IV** and **VI** can then be
converted to **V** and **VII**, respectively, employing the acylating
methodology described above.

10

15

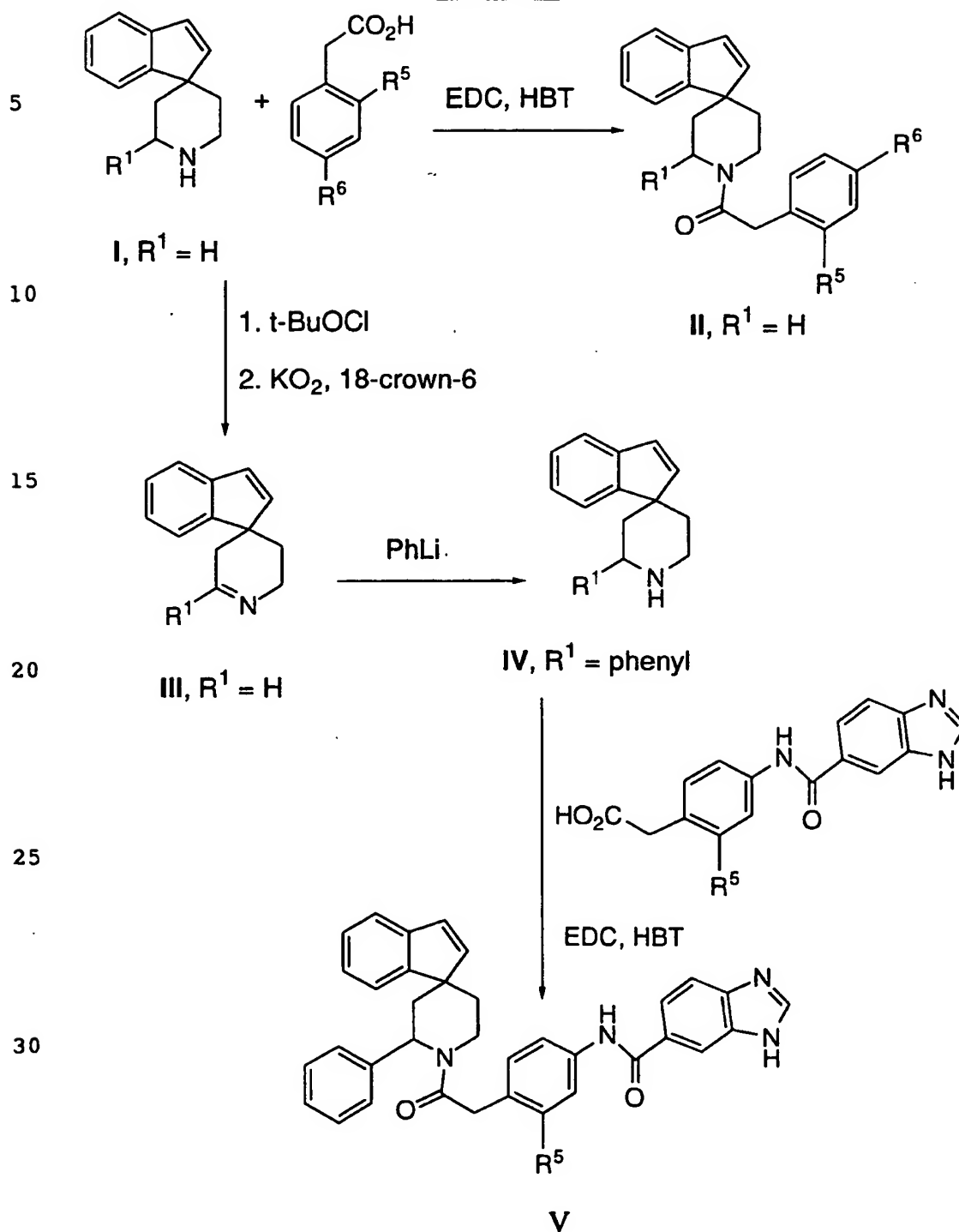
20

25

30

- 29 -

SCHEME I

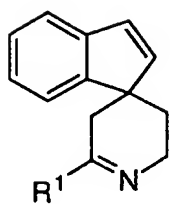


- 30 -

SCHEME I (CONT'D)

5

10

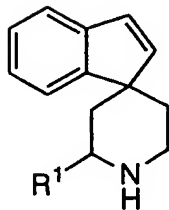
III, $R^1 = H$

15

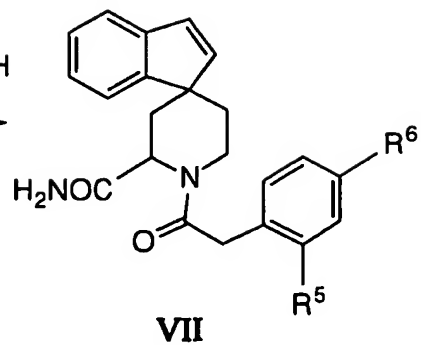
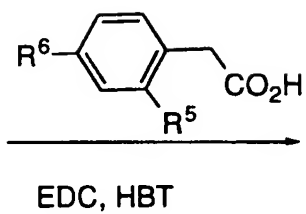
1. TMSCN

2. H_2O_2 , NaOH

20



25

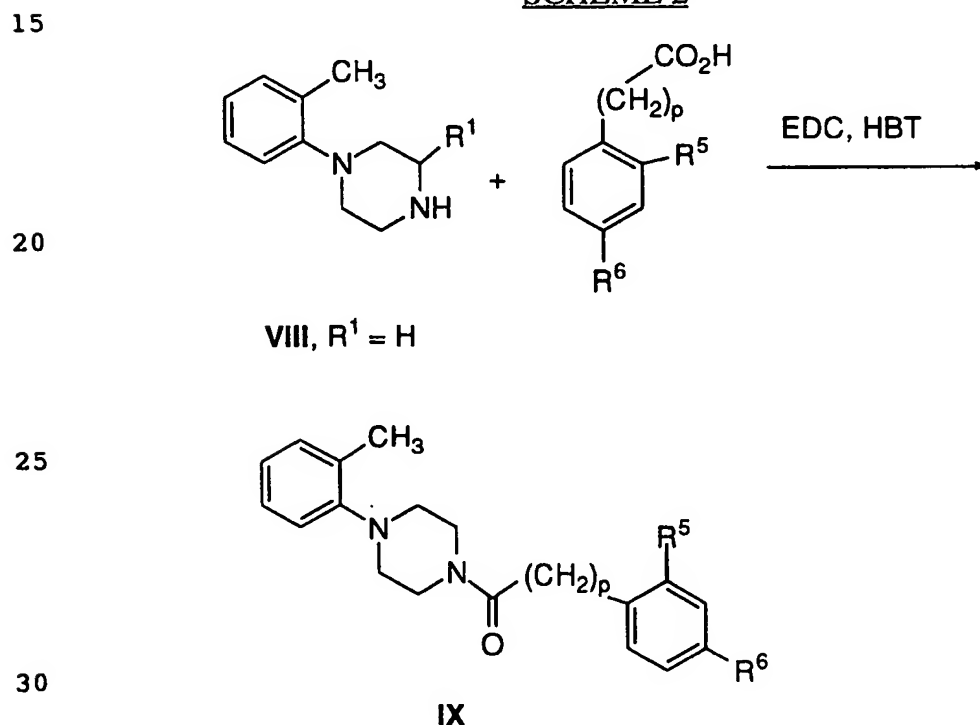
VI, $R^1 = CONH_2$ 

VII

30

- 31 -

The compounds of the present invention are also prepared as outlined in Scheme 2, wherein 1-(2-tolyl)piperazine **VIII** is acylated with a carboxylic acid derivative, preferably a phenylacetic acid analog, according to common amide bond forming techniques. A preferred method consists of adding the water soluble reagent (EDC) and an activating agent like (HBT) to a solution of DMF, at ambient temperature, containing 1-(2-tolyl)piperazine and a phenylacetic acid analog. The reaction mixture temperature is maintained at 23°C, and the pH is monitored throughout the course of the reaction and is adjusted when necessary to approximately 8 with a trialkylamine base like (TEA) or diisopropylethylamine (DIEA). Extractive workup and standard purification yields the product **IX**.

SCHEME 2

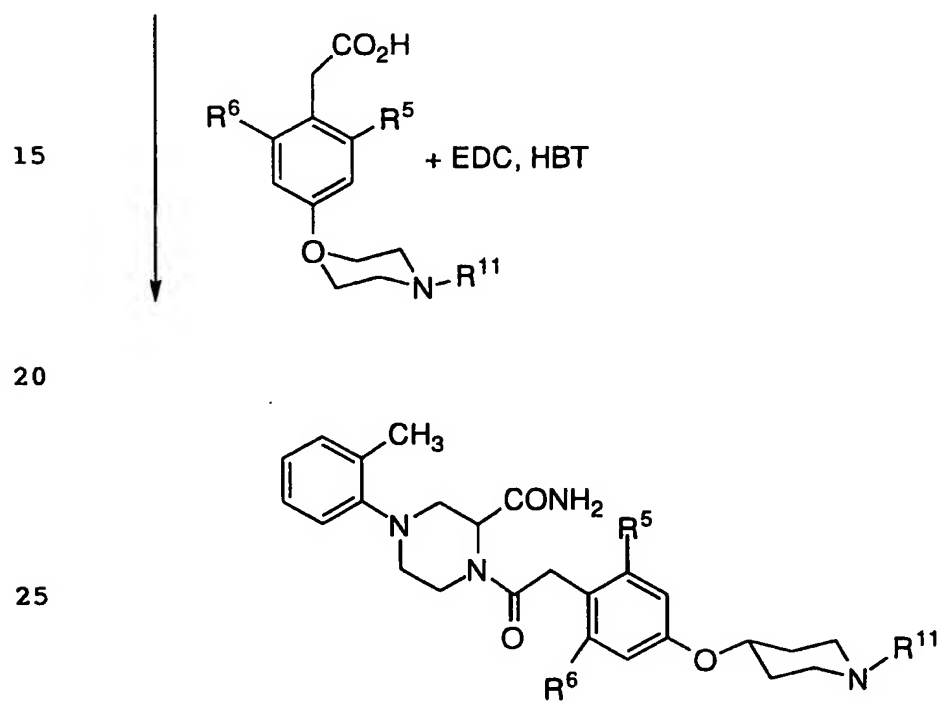
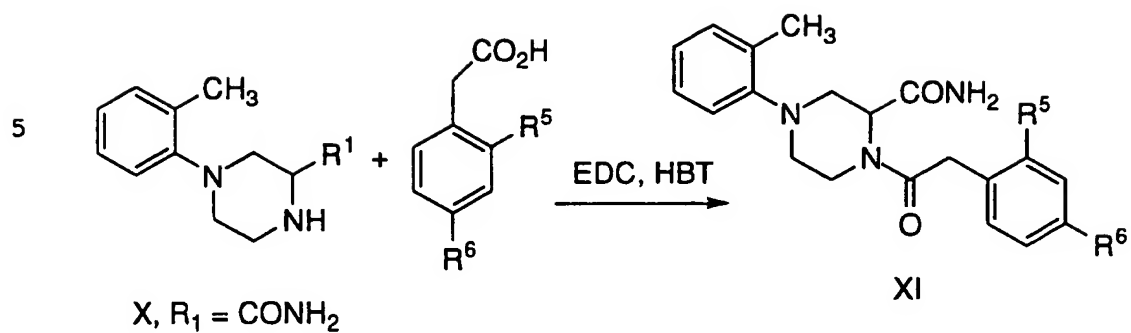
- 32 -

A further method for preparing the compounds of the present invention is shown in Scheme 3 and consists of reacting 4-(2-methylphenyl)piperazine-2-carboxamide **X** (prepared either according to the procedure in *J. Med. Chem.* **1992**, 35, 743-750 or in
5 *Tetrahedron Letters*, **1988**, 29(52), 6913-6916) with a carboxylic acid derivative, preferably a phenylacetic acid analog, according to common amide bond forming techniques to give **XI** and **XII**. The latter compound is then further elaborated at the piperidinol nitrogen by
10 acylation, for example with 3,4-diethoxy-3-cyclobutene-1,2-dione to afford **XIII** or with imidazole acetic acid to yield **XV**. The piperidinol nitrogen atom can also be alkylated with a suitable alkylating agent, for example picolyl chloride, in an appropriate solvent like DMF, in the presence of an inorganic base or preferably a trialkylamine base like
15 TEA or DIEA to afford **XIV**. The terminal piperidinol nitrogen atom in **XII** can also be sulfonylated with a sulfonyl chloride derivative, for example with chloroethylsulfonyl chloride, in an organic solvent, preferably ethyl acetate or methylene chloride using a base, preferably DIEA. The resulting sulfonamide derivative is then converted to the
20 desired product **XVI** using standard synthetic methodology.

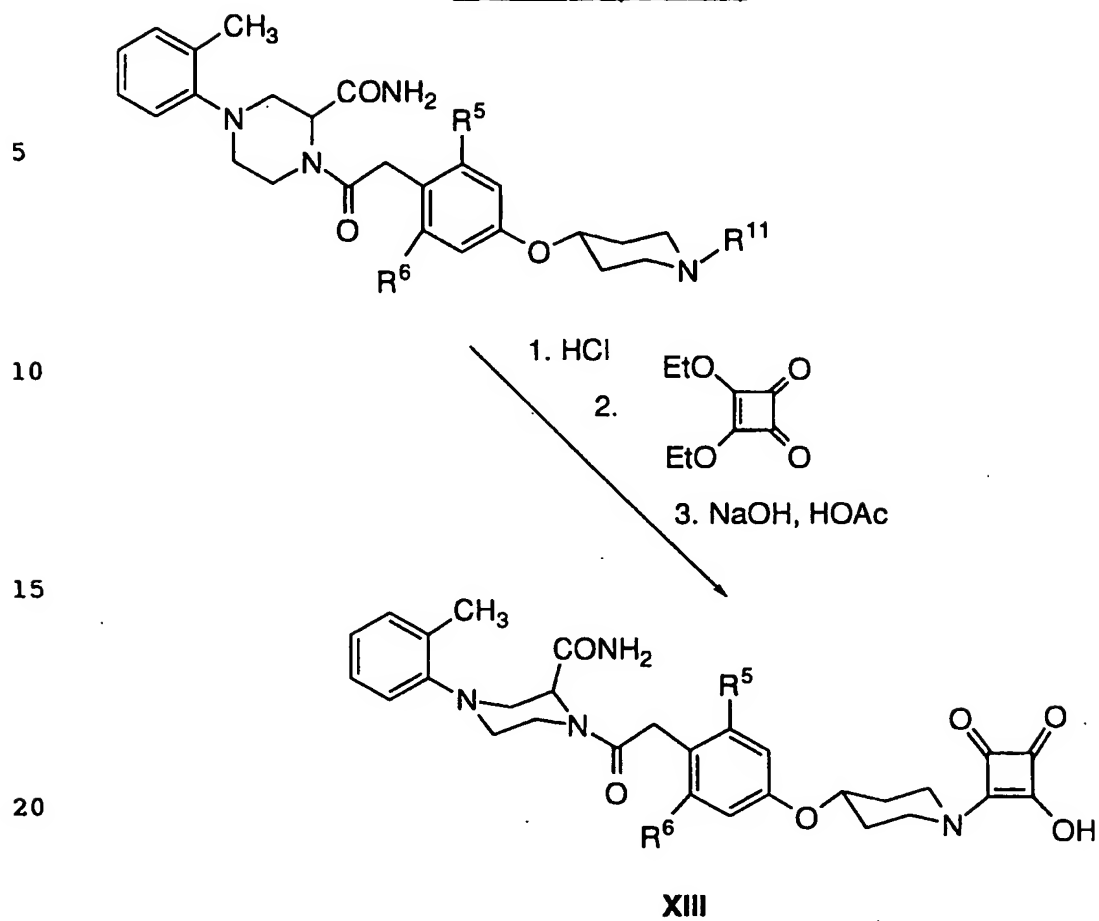
25

30

- 33 -

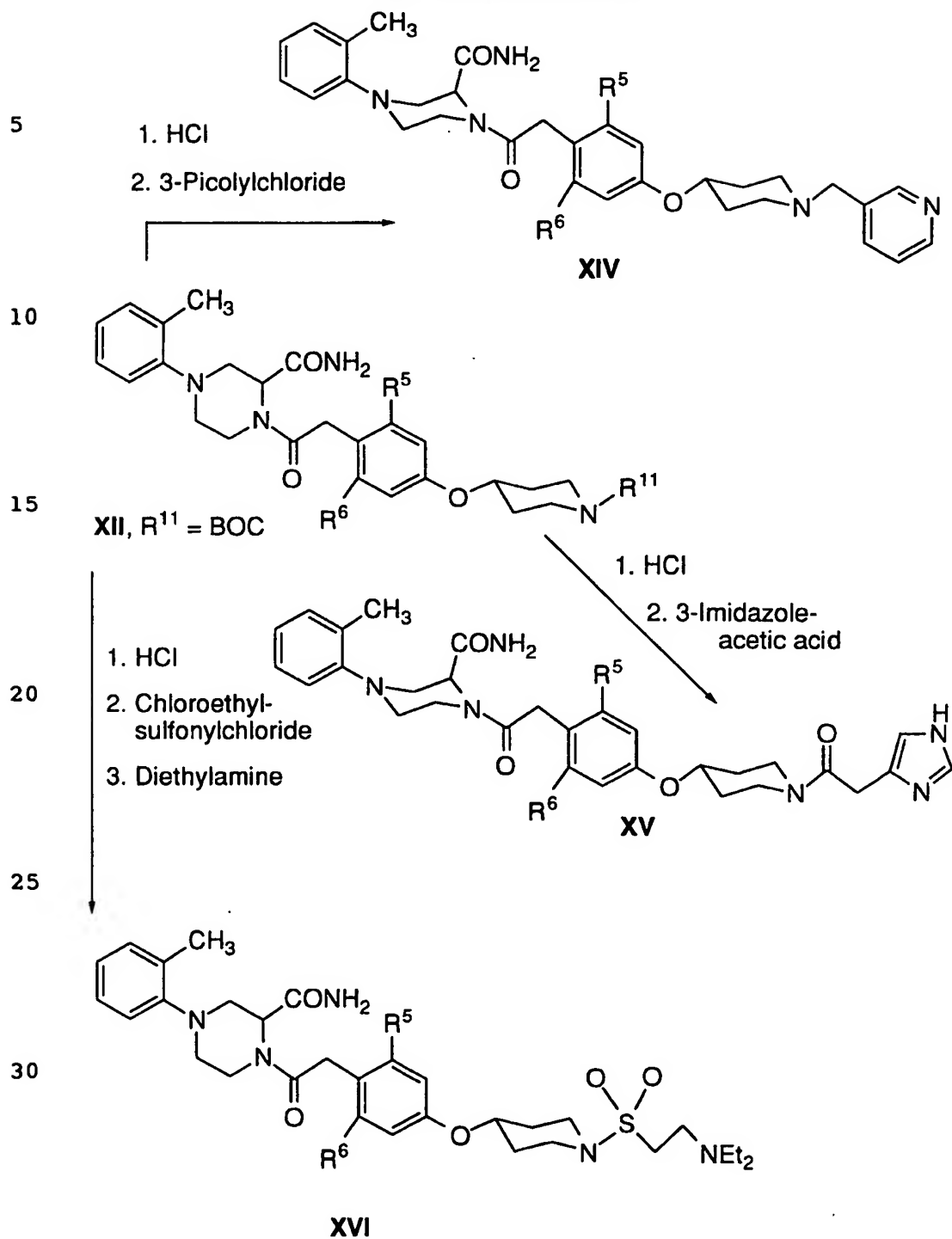
SCHEME 3

- 34 -

SCHEME 3 (CONT'D)

- 35 -

SCHEME 3 (CONT'D)

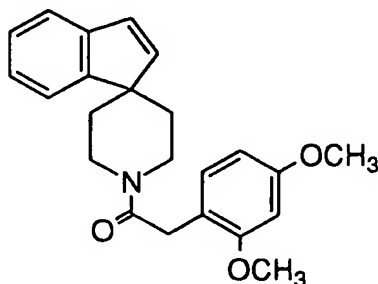


- 36 -

EXAMPLE 11'-(2,4-Dimethoxyphenylacetyl)-spiro[1H]indene-1,4'-piperidine

5

10



15

20

25

Spiro[1H]indene-1,4'-piperidine hydrochloride (100 mg, 0.45 mmol) was dissolved in DMF (2 ml) and treated with 2,4-dimethoxy-phenylacetic acid (97.3 mg, 0.5 mmol), EDC (95 mg, 0.5 mmol), and HBT (67 mg, 0.5 mmol). The pH of the mixture was adjusted to ca. 9.5 (moistened E. Merck colorpHast indicator) with triethylamine, and the mixture was stirred at ambient temperature for 18 hours. The solvent was removed in vacuo and the residue was treated with water and extracted with ethyl acetate. The combined ethyl acetate layers were washed with brine, dried over sodium sulfate, filtered, and evaporated to dryness in vacuo. The residue was chromatographed on silica gel eluted with 8% ether in methylene chloride. The combined product fractions were evaporated to dryness in vacuo and the residue crystallized from ether to give 1'-(2,4-dimethoxyphenylacetyl)-spiro[1H]indene-1,4'-piperidine: mp 93-108°C.

30

¹H-NMR: Consistent with structure

TLC: silica gel, 10% ether in methylene chloride: single component, R_f = 0.41

FABMS: M+H @ m/e = 364

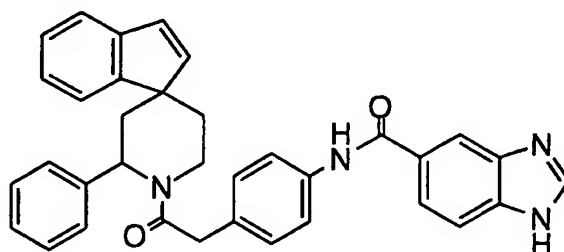
HPLC: 98%

Anal. cal'd for C₂₃H₂₅NO₃•0.55 H₂O:

C, 73.98; H, 7.05, N, 3.75.

Found: C, 73.70; H, 7.30; N, 4.04.

- 37 -

EXAMPLE 21'-(4-(Benzimidazole-5-carboxylamino)phenylacetyl)-2'-phenyl-
spiro[1H]indene-1,4'-piperidine3',4',5',6'-Tetrahydrospiro[1H]indene-1,4'-pyridine

Spiro[1H]indene-1,4'-piperidine hydrochloride (5 g, 22.6 mmol) was partitioned between saturated aqueous sodium bicarbonate and ether. The aqueous layer was extracted with ether. The combined ether layers were dried over sodium sulfate, filtered, and concentrated in vacuo to 50 ml. The solution of spiro[1H]indene-1,4'-piperidine was cooled in ice and treated with t-butyl hypochlorite (3.37 ml, 3.06 g, 28.2 mmol). The mixture was stirred in the cold for 30 min. An additional 1.0 ml of t-butyl hypochlorite was added and the mixture stirred another 15 min. A final 0.5 ml portion of t-butyl hypochlorite was added and the mixture stirred an additional 15 min. The ether layer was washed with water, with dilute sulfuric acid, with water, and with brine, dried over magnesium sulfate, filtered, and concentrated in vacuo to 10 ml. The solution was re-dried over magnesium sulfate and calcium carbonate for 1 hour, then filtered directly into an ether suspension of potassium superoxide (3.53 g, 49.7 mmol) and 18-crown-6 (100 mg). The mixture was stirred 4.5 hours at ambient temperature, then filtered and diluted with ether to 75 ml to provide a solution of 3',4',5',6'-tetrahydrospiro[1H]indene-1,4'-pyridine of nominal 0.3 M concentration.

2'-Phenyl-spiro[1H]indene-1,4'-piperidine

- 38 -

3',4',5',6'-Tetrahydrospiro[1H]indene-1,4'-pyridine (15 ml of 0.3 M ether solution; 4.5 mmol) was added to phenyllithium solution (5.27 ml of 1.8 M solution in 70/30 cyclohexane/ether, 9.5 mmol) stirred in an ice bath. The mixture was stirred 30 min. in the cold, then
5 18 hours at ambient temperature. Water was added, and the mixture extracted with ether. The combined ether layers were washed with water, then with brine, dried over sodium sulfate, filtered, and evaporated to dryness in vacuo. The residue was chromatographed on silica gel eluted with 90:7:0.7:0.7 methylene
10 chloride:methanol:water:acetic acid. The combined product fractions were evaporated to dryness, and the residue was rechromatographed on silica gel eluted with 80:4:0.4 methylene chloride:methanol:concentrated ammonia. The product fractions were evaporated to dryness in vacuo
15 to give 2'-phenyl-spiro[1H]indene-1,4'-piperidine.

4-(Benzimidazole-5-carboxylamino)phenylacetic acid

Methyl 4-aminophenylacetate hydrochloride (6.9 g, 34 mmol), benzimidazole-5-carboxylic acid (5.0 g, 31 mmol), EDC (9.0 g, 47 mmol) and HBT (6.4 g, 47 mmol) were combined in DMF (250
20 ml). The pH of the mixture was adjusted to ca. 9 with diisopropylethylamine, and the mixture was stirred at ambient temperature for 3 days. The solvent was removed in vacuo, and the residue was treated with aqueous sodium bicarbonate and extracted with ethyl acetate. The combined ethyl acetate layers were washed with
25 water and with brine, dried over sodium sulfate, filtered, and evaporated to dryness in vacuo to give methyl 4-(benzimidazole-5-carboxylamino)phenylacetate.

Methyl 4-(benzimidazole-5-carboxylamino)phenylacetate (3.6 g, 12 mmol) was dissolved in methanol (50 ml) and treated with aqueous sodium hydroxide (4.8 g, 120 mmol, in 50 ml of water) and stirred at ambient temperature for 2 hours. The mixture was concentrated in vacuo and the residue acidified with concentrated HCl. The mixture was filtered to give 4-(benzimidazole-5-carboxylamino)phenylacetic acid.

- 39 -

1'-(4-(Benzimidazole-5-carboxylamino)phenylacetyl)-2'-phenyl-spiro[1H]indene-1,4'-piperidine

2'-Phenyl-spiro[1H]indene-1,4'-piperidine (55 mg, 0.21 mmol) was dissolved in DMF (1 ml) and treated with 4-(benzimidazole-5-carboxylamino)phenylacetic acid (93.2 mg, 0.316 mmol), EDC (605. mg, 0.316 mmol) and HBT (42.7 mg, 0.316 mmol). The pH of the mixture was adjusted to ca. 9.5 (moistened E. Merck colorpHast indicator) with triethylamine, and the mixture was stirred at ambient temperature for 18 hours. The solvent was removed in vacuo and the residue treated with aqueous sodium bicarbonate and extracted with ethyl acetate. The combined ethyl acetate layers were washed with brine, dried over sodium sulfate, filtered, and evaporated to dryness in vacuo. The residue was chromatographed on silica gel eluted with 115:10:1 methylene chloride:methanol:concentrated ammonia. The combined product fractions were evaporated to dryness in vacuo and the residue triturated with ether to give 1'-(4-(benzimidazole-5-carboxylamino)phenylacetyl)-2'-phenyl-spiro[1H]indene-1,4'-piperidine: mp 175-188°C.

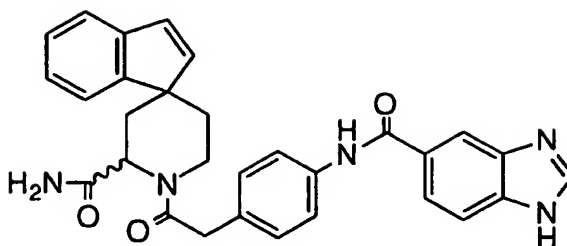
¹H-NMR: Consistent with structure
TLC: silica gel, 115:10:1 methylene chloride:methanol:concentrated ammonia: single component, R_f= 0.30
FABMS: M+H @ m/e= 539
HPLC: 95%
Anal. cal'd for C₃₅H₃₀N₄O₂•0.1C₄H₁₀O•0.3CH₂Cl₂•0.2 H₂O:
C, 74.55 H, 5.61 N, 9.74.
Found: C, 74.26; H, 5.74; N, 9.48.

EXAMPLE 3

1'-(4-(Benzimidazole-5-carboxylamino)phenyl-acetyl)-spiro[1H]indene-1,4'-piperidine-2'-carboxamide diastereomer A and diastereomer B

- 40 -

5



2'-Cyano-spiro[1H]indene-1,4'-piperidine

10

3',4',5',6'-Tetrahydrospiro[1H]indene-1,4'-pyridine (21 ml of 0.22 M ether solution; 4.6 mmol) was added slowly to a solution of trimethylsilylcyanide (1.32 ml, 0.984 g, 9.92 mmol) stirred in ether in an ice bath. The mixture was stirred in the cold for 30 min, then at ambient temperature for 18 hours. The solution was washed with water and with brine, dried over sodium sulfate, filtered, and evaporated to dryness in vacuo. The residue was chromatographed on silica gel eluted with 20% ether in methylene chloride. The combined product fractions were evaporated to dryness in vacuo and the residue was crystallized from ether/hexane to give 2'-cyano-spiro[1H]indene-1,4'-piperidine.

20

Spiro[1H]indene-1,4'-piperidine-2'-carboxamide

2'-Cyano-spiro[1H]indene-1,4'-piperidine (2.0 g, 9.5 mmol) was dissolved in 95% ethanol (21 ml) and treated with 10% aqueous sodium hydroxide (1 ml, 2.5 mmol) followed by 30% aqueous hydrogen peroxide (1.08 ml, 9.5 mmol). The mixture was stirred in an ice bath for 10 min, at ambient temperature for 30 min, then at 50°C (oil bath) for 2.5 hours. The mixture was poured into water (200 ml) and extracted with methylene chloride. The combined organic layers were washed with 10% aqueous sodium bisulfite, dried over sodium sulfate, filtered, and evaporated to dryness in vacuo. The residue was chromatographed on silica gel eluted with 90:20:2:2 methylene chloride:methanol:water:acetic acid. The separated fractions were evaporated to dryness in vacuo to give the individual diastereomers A and B of spiro[1H]indene-1,4'-piperidine-2'-carboxamide.

30

- 41 -

1'-(4-(Benzimidazole-5-carboxylamino)phenylacetyl)-spiro[1H]indene-1,4'-piperidine-2'-carboxamide, diastereomer A

5 Spiro[1H]indene-1,4'-piperidine-2'-carboxamide, diastereomer A (45 mg, 0.2 mmol), 4-(benzimidazole-5-carboxylamino)phenylacetic acid (64 mg, 0.22 mmol), EDC (41.6 mg, 0.22 mmol), and HBT (29.3 mg, 0.22 mmol) were combined in DMF (2 ml). The mixture was adjusted to pH ca. 9.5 (moistened E. Merck colorpHast indicator) with triethylamine and stirred at ambient
10 temperature for 18 hours. The solvent was removed in vacuo and the residue was treated with water and extracted with ethyl acetate containing 10% n-butanol. The combined organic layers were washed with brine, dried over sodium sulfate, filtered, and evaporated to dryness in vacuo. The residue was chromatographed on silica gel eluted with 80:10:1 methylene chloride:methanol:concentrated ammonia. The
15 combined product fractions were evaporated to dryness in vacuo and the residue crystallized from ether to give 1'-(4-(benzimidazole-5-carboxylamino)phenylacetyl)-spiro[1H]indene-1,4'-piperidine-2'-carboxamide, diastereomer A: mp 185-207°C.

20 ¹H-NMR: Consistent with structure
TLC: silica gel, 80:10:1 methylene chloride:methanol:concentrated ammonia: single component, R_f = 0.30

FABMS: M+H @ m/e = 506

25 HPLC: 88%

Anal. cal'd for C₃₀H₂₇N₅O₃•1.3 H₂O:

C, 68.11; H, 5.64; N, 13.24.

Found: C, 67.97; H, 5.54; N, 12.95.

30 1'-(4-(Benzimidazole-5-carboxylamino)phenylacetyl)-spiro[1H]indene-1,4'-piperidine-2'-carboxamide, diastereomer B

The procedure described for preparation of 1'-(4-(Benzimidazole-5-carboxylamino)phenylacetyl)-spiro[1H]indene-1,4'-piperidine-2'-carboxamide, diastereomer A was carried out using

- 42 -

spiro[1H]indene-1,4'-piperidine-2'-carboxamide, diastereomer B in place of spiro[1H]indene-1,4'-piperidine-2'-carboxamide, diastereomer A. Chromatography was with 100:10:1 methylene chloride:methanol: concentrated ammonia. The combined product fractions were
5 evaporated to dryness in vacuo and the residue crystallized from ether to give 1'-(4-(benzimidazole-5-carboxylamino)phenylacetyl)-spiro[1H]indene-1,4'-piperidine-2'-carboxamide, diastereomer B: mp 181-202°C.

10 ¹H-NMR: Consistent with structure
TLC: silica gel, 80:10:1 methylene chloride:methanol:concentrated ammonia: single component, R_f= 0.25

FABMS: M+H @ m/e= 506

15 HPLC: 98%

Anal. cal'd for C₃₀H₂₇N₅O₃•1.3 H₂O:

C, 68.11; H, 5.64; N, 13.24.

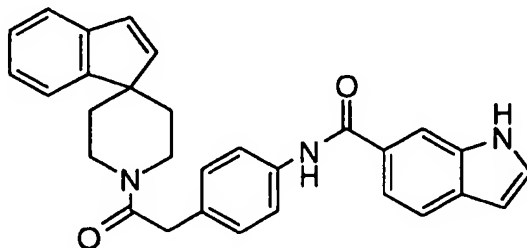
Found: C, 68.03; H, 4.83; N, 13.07.

20

EXAMPLE 4

1'-(4-(Indole-6-carboxylamino)phenylacetyl)spiro[1H]indene-1,4'-piperidine

25



30

Spiro[1H]indene-1,4'-piperidine hydrochloride (2.8 g, 12.6 mmol) was dissolved in DMF (40 ml) and treated with 4-aminophenylacetic acid (2.1 g, 13.9 mmol) followed by BOP reagent (6.13 g, 13.9 mmol). Diisopropylethylamine was added to adjust the pH

- 43 -

of the mixture to ca. 9.5 (moistened E. Merck colorpHast indicator). The mixture was stirred at ambient temperature for 1 hour, then concentrated in vacuo. The residue was treated with water and extracted with ethyl acetate. The combined organic layers were washed with water, then with brine, dried over sodium sulfate, filtered, and evaporated to dryness in vacuo. The residue was chromatographed on silica gel eluted with 65:35 ethyl acetate:methylene chloride. The product fractions were combined and evaporated to dryness to give 1'-(4-aminophenylacetyl)spiro[1H]indene-1,4'-piperidine.

1'-(4-aminophenylacetyl)spiro[1H]indene-1,4'-piperidine (104 mg, 0.33 mmol), indole-6-carboxylic acid (58 mg, 0.36 mmol; prepared as described in US 4,894,386), EDC (68.8 mg, 0.36 mmol), and HBT (48.6 mg, 0.36 mmol) were combined in DMF (2 ml) and treated with triethylamine to bring the pH of the mixture (moistened E. Merck colorpHast indicator) to ca. 9.5. The mixture was stirred at ambient temperature for 5 days. The solvent was removed in vacuo and the residue was diluted with water and extracted with ethyl acetate. The combined organic layers were washed with brine, dried over sodium sulfate, filtered, and evaporated to dryness in vacuo. The residue was chromatographed on silica gel eluted with 266:10:1 methylene chloride:methanol:concentrated ammonia. The combined product fractions were evaporated to dryness in vacuo, and the residue was crystallized from ethyl acetate to give 1'-(4-(indole-6-carboxylamino)-phenylacetyl)spiro[1H]indene-1,4'-piperidine: mp 259-262°C.

¹H-NMR: Consistent with structure

TLC: silica gel, 266:10:1 methylene

chloride:methanol:concentrated ammonia: single component, R_f = 0.20

FABMS: M+H @ m/e = 462 (free base)

HPLC: 95%

- 44 -

Anal. cal'd for $C_{30}H_{27}N_3O_2 \cdot 0.1EtOAc \cdot 0.15 H_2O$:

C, 77.18 H, 5.99 N, 8.88.

Found: C, 76.89; H, 5.97; N, 8.92.

5

EXAMPLE 5

1-Benzyl-4-(2-methylphenyl)piperazine-2-carboxamide

10



15

2-Benzylaminoethanol (18.8 ml, 20 g, 0.13 mol) was converted to N-(2-chloroethyl)-N-benzylamine hydrochloride with thionyl chloride (19 ml, 31 g, 0.26 mol) according to the procedure described in J. Chem. Soc. 1955, 896. N-(2-chloroethyl)-N-benzylamine hydrochloride (4.0 g, 19 mmol) was converted to N-benzyl-N'-(2-methylphenyl)-1,2-diaminoethane hydrochloride by the procedure of Syn. Comm. 18, 45-50 (1988), using o-toluidine (6.1 ml, 6.1 g, 57 mmol) in place of aniline. 1-benzyl-4-(2-methylphenyl)-piperazine-2-carboxamide was prepared from 2,3-dibromopropionamide (7.9 g, 34 mmol) by the procedure of J. Med. Chem. 35, 743-750 (1992) using N-benzyl-N'-(2-methylphenyl)-1,2-diaminoethane hydrochloride (4.95 g, 18 mmol) in place of N-benzyl-N'-phenyl-1,2-diaminoethane hydrochloride.

30

¹H-NMR: Consistent with structure

TLC: silica gel, 5% methanol in methylene chloride:
single component, R_f = 0.51

FABMS: M+H @ m/e = 310

- 45 -

HPLC: 98%

Anal. cal'd for C₁₉H₂₃N₃O·0.2 H₂O:

C, 72.90; H, 7.54; N, 13.43.

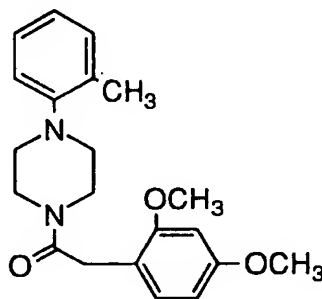
Found: C, 72.83; H, 7.29; N, 13.53.

5

EXAMPLE 61-(2,4-Dimethoxyphenylacetyl)-4-(2-methylphenyl)piperazine

10

15



20

25

30

1-(2-methylphenyl)piperazine (.087 g, 0.41 mmol) and 2,4-dimethoxyphenylacetic acid (0.096 g, 0.49 mmol) were dissolved in DMF (5 ml) and treated with EDC (0.091 g, 0.47 mmol) and HBT (0.071 g, 0.52 mmol). Triethylamine was added to the stirred mixture to bring the pH (moistened E. Merck colorpHast indicator) to ca. 9. The mixture was stirred at ambient temperature for 18 hours, then concentrated in vacuo. The residue was taken up in ethyl acetate, and the ethyl acetate layer was washed with saturated aqueous sodium bicarbonate and brine, dried over sodium sulfate, filtered, and the filtrate was concentrated to dryness in vacuo. The residue was chromatographed on silica gel eluted with 1.5% methanol in methylene chloride. The combined product fractions were evaporated to dryness in vacuo to give the title compound.

¹H-NMR: Consistent with structure

TLC: silica gel, 5% methanol in methylene chloride:

single component, R_f = 0.72

FABMS: M+H @ m/e = 355

- 46 -

HPLC: 96%

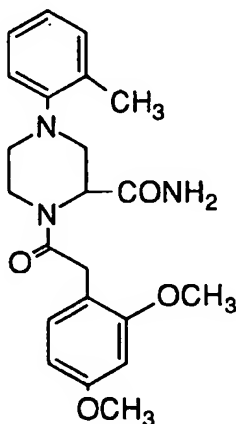
Anal. cal'd for $C_{21}H_{26}N_2O_3 \cdot 0.05 Et_2O \cdot 0.55 H_2O$:

C, 69.18; H, 7.56; N, 7.61.

Found: C, 69.15; H, 7.31; N, 7.75.

EXAMPLE 7

1-(2,4-Dimethoxyphenylacetyl)-4-(2-methylphenyl)piperazine-2-carboxamide



1-benzyl-4-(2-methylphenyl)piperazine-2-carboxamide (2.64 g, 8.53 mmol) and palladium hydroxide/carbon (430 mg) were combined in a mixture of methanol (35 ml) and ethanol (35 ml) and shaken in an atmosphere of hydrogen at 55 psi for 6 hours at ambient temperature. The mixture was filtered and the filtrate was concentrated in vacuo. The residue was reconcentrated in vacuo from ether three times to provide 4-(2-methylphenyl)piperazine-2-carboxamide.

4-(2-Methylphenyl)piperazine-2-carboxamide (39 mg, 0.18 mmol), 2,4-dimethoxyphenylacetic acid (42 mg, 0.21 mmol), EDC (42 mg, 0.22 mmol) and HBT (31 mg, 0.23 mmol) were combined in DMF (5 ml) and treated with triethylamine to adjust the pH to ca. 9 (moistened E. Merck colorpHast indicator). The mixture was stirred at ambient temperature for 64 hours. The solvent was removed in vacuo and the residue was chromatographed on silica gel eluted with 2%

- 47 -

methanol in methylene chloride. The combined product fractions were evaporated to dryness in vacuo to provide the title compound.

¹H-NMR: Consistent with structure

5 TLC: silica gel, 5% methanol in methylene chloride:
single component, R_f = 0.45

FABMS: M+H @ m/e = 398

HPLC: 99%

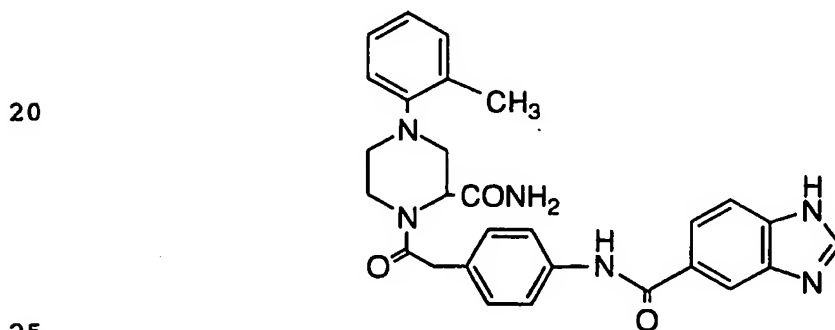
Anal. cal'd for C₂₂H₂₇N₃O₄:

10 C, 66.48; H, 6.85; N, 10.57.

Found: C, 66.54; H, 6.91; N, 10.36.

EXAMPLE 8

15 1-(4-(Benzimidazol-5-carboxylamino)phenylacetyl)-4-(2-methylphenyl)piperazine-2-carboxamide



4-(2-Methylphenyl)piperazine-2-carboxamide (0.123 g, 0.56 mmol), 4-(benzimidazol-5-carboxylamino)phenylacetic acid (204 mg, 0.69 mmol), EDC (131 mg, 0.68 mmol) and HBT (96 mg, 0.71 mmol) were combined in DMF (5 ml) and treated. Triethylamine was added to the stirred mixture to bring the pH (moistened E. Merck colorpHast indicator) to ca. 9. The mixture was stirred at ambient temperature for 18 hours, then concentrated in vacuo. The residue was taken up in ethyl acetate, and the ethyl acetate layer was washed with saturated aqueous sodium bicarbonate and brine, dried over sodium sulfate, filtered, and the filtrate was concentrated to dryness in vacuo.

30

- 48 -

The residue was chromatographed on silica gel eluted with 92:8:0.8 methylene chloride:methanol:concentrated ammonia. The combined product fractions were evaporated to dryness in vacuo and the residue was reconcentrated from ether, then triturated with ether and filtered to give the title compound.

¹H-NMR: Consistent with structure

TLC: silica gel, 95:5:0.5 methylene

chloride:methanol:concentrated ammonia: single component, $R_f = 0.29$

FABMS: M+H @ m/e= 497

HPLC: 97%

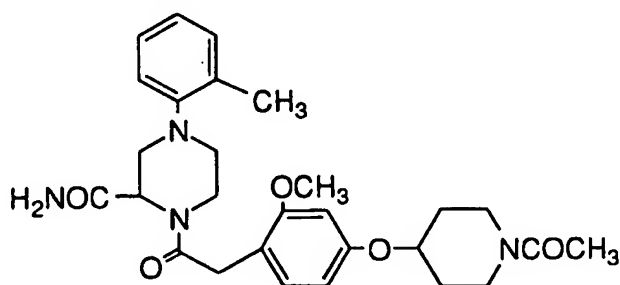
Anal. cal'd for $C_{28}H_{28}N_6O_3 \cdot 0.2 Et_2O \cdot 0.6 H_2O$:

C, 66.24; H, 6.02; N, 16.09.

Found: C, 66.26; H, 5.91; N, 15.83.

EXAMPLE 9

1-(2-Methoxy-4-(1-acetyl-4-piperidyloxy)phenylacetyl)-4-(2-methylphenyl)piperazine-2-carboxamide



4-Hydroxypiperidine (15.52 g, 0.153 mol) in methylene chloride (100 ml) was treated with a solution of di-*t*-butyl dicarbonate (33.2 g, 0.152 mol) in methylene chloride (100 ml) added dropwise over 20 min. The mixture was stirred at ambient temperature for 3 hours, then evaporated to dryness in vacuo. The residue was concentrated from ether to give 1-Boc-4-hydroxypiperidine.

- 49 -

Methyl 2,4-dihydroxybenzoate (5.1 g, 30.33 mmol) and triphenylphosphine (9.52 g, 36.3 mmol) were stirred in THF (200 ml) under nitrogen. The mixture was cooled in an ice bath and treated with a solution of 1-Boc-4-hydroxypiperidine (6.8 g, 33.8 mmol) and diethyl azodicarboxylate (5.73 ml, 6.34 g, 36.4 mmol) in THF (100 ml) added dropwise over 30 min. The mixture was stirred at ambient temperature for 18 hours, then diluted with ethyl acetate and washed with 1M NaOH, saturated aqueous sodium bicarbonate, and brine. The organic layer was dried over sodium sulfate, filtered, and evaporated to dryness in vacuo. The residue was chromatographed on silica gel eluted with 10% ethyl acetate in hexane, and the product fractions were evaporated to dryness in vacuo to give methyl 2-hydroxy-4-(1-Boc-4-piperidyloxy)benzoate.

Methyl 2-hydroxy-4-(1-Boc-4-piperidyloxy)benzoate (6.7 g, 19.1 mmol) was dissolved in THF (20 ml) and stirred in an ice bath under nitrogen. Sodium hydride (1.17g of a 60% suspension in mineral oil, 29.5 mmol) was added and the mixture was stirred for 15 min in the cold, then for 15 min at ambient temperature. Iodomethane (2.4 ml, 5.47 g, 38.1 mmol) was added and the mixture was allowed to stir at ambient temperature under nitrogen for 72 hours. An additional 0.51 g of 60% sodium hydride suspension was added and the mixture stirred an additional 7 hours, then an additional 1.2 ml of iodomethane was added and the mixture stirred another 18 hours. An additional 0.53 g of sodium hydride suspension was added, the mixture was stirred 1.5 hours, then an additional 1 ml of iodomethane was added and the mixture stirred 6 hours. An additional 1 ml of iodomethane was added and the mixture stirred 18 hours at ambient temperature. The mixture was diluted with ethyl acetate and washed with saturated aqueous sodium bicarbonate and with brine. The organic layer was dried over sodium sulfate, filtered, and evaporated to dryness in vacuo to give methyl 2-methoxy-4-(1-Boc-4-piperidyloxy)-benzoate.

Methyl 2-methoxy-4-(1-Boc-4-piperidyloxy)benzoate (4.5 g, 12.3 mmol) was dissolved in THF (200 ml) and treated with a solution of lithium hydroxide (17 ml of a 1.1M aqueous solution, 18.7

- 50 -

mmol) added over 5 min. The mixture was stirred at ambient temperature for 72 hours. An additional 4 ml of 1.1M lithium hydroxide was added and the mixture was heated at reflux for 13 hours, then stirred at ambient temperature for 18 hours. The reaction mixture
5 was concentrated in vacuo and the residue partitioned between ethyl acetate and 1N hydrochloric acid. The organic layer was washed with brine, dried over sodium sulfate, filtered, and evaporated to dryness in vacuo to give 2-methoxy-4-(1-Boc-4-piperidyloxy)benzoic acid.

2-Methoxy-4-(1-Boc-4-piperidyloxy)benzoic acid (0.79 g,
10 2.24 mmol) was dissolved in ethyl acetate (15 ml). The solution was cooled in ice and saturated with HCl gas, then stirred 30 min in the cold. The mixture was evaporated in vacuo and the residue concentrated from ether three times to give 2-methoxy-4-(4-piperidyloxy)benzoic acid.

2-Methoxy-4-(4-piperidyloxy)benzoic acid (0.6 g, 2.09
15 mmol) was stirred in THF (10 ml) and treated with triethylamine (0.29 ml, 0.21 g, 2.08 mmol), followed by acetyl chloride (0.18 ml, 0.2 g, 2.5 mmol) and an additional 0.35 ml of triethylamine. The mixture was stirred at ambient temperature for 18 hours, then concentrated in vacuo.
20 The residue was partitioned between aqueous sodium bicarbonate and ethyl acetate. The ethyl acetate layer was extracted with sodium bicarbonate solution. The combined sodium bicarbonate layers were acidified with 1N HCl and extracted with ethyl acetate. The organic layers were combined, washed with brine, dried over sodium sulfate,
25 filtered, and evaporated to dryness in vacuo to give 2-methoxy-4-(1-acetyl-4-piperidyloxy)benzoic acid.

2-Methoxy-4-(1-acetyl-4-piperidyloxy)benzoic acid (0.546
g, 1.86 mmol) in THF (10 ml) was stirred under nitrogen and treated with thionyl chloride (0.27 ml, 0.44 g, 3.7 mmol). The mixture was
30 stirred at ambient temperature for 18 hours, then concentrated in vacuo to give 2-methoxy-4-(1-acetyl-4-piperidyloxy)benzoyl chloride.

A mixture of ether (14 ml) and 40% aqueous potassium hydroxide (4.2 ml) was cooled in ice. N-Nitrosomethylurea (1.4g) was added in portions with gentle swirling over 30 min. The ether layer was decanted and dried over solid potassium hydroxide for 15 min.

- 51 -

The ether solution was decanted, then cooled in an ice bath. A solution of 2-methoxy-4-(1-acetyl-4-piperidyloxy)benzoyl chloride (0.58 g, 1.86 mmol) in THF (3 ml) was added dropwise and the mixture was stirred at ambient temperature for 2 hours. Nitrogen was passed through the mixture for 1 hour, and the solution was then concentrated in vacuo. The residue was dissolved in methanol and treated with freshly prepared silver oxide (48 mg), and the mixture was heated at reflux for 30 min. Three additional lots of 100 mg of silver oxide were added with 1 hour reflux following each. The mixture was cooled and filtered, and the filtrate was concentrated in vacuo. The residue was chromatographed on silica gel eluted with 2%, followed by 4% methanol in methylene chloride. The product fractions were combined and evaporated to dryness in vacuo to give methyl 2-methoxy-4-(1-acetyl-4-piperidyloxy)phenylacetate.

Methyl 2-methoxy-4-(1-acetyl-4-piperidyloxy)phenylacetate (0.18 g, 0.56 mmol) was dissolved in THF (5 ml) and treated with lithium hydroxide (0.67 ml of a 1 M aqueous solution, 0.67 mmol). The mixture was stirred at ambient temperature for 4 hours, then treated with an additional 0.2 ml of 1 M lithium hydroxide. The mixture was heated at 60° for 6 hours, then cooled and concentrated in vacuo. The residue was acidified with 1M HCl, and extracted with ethyl acetate. The combined ethyl acetate layers were extracted with saturated aqueous sodium carbonate. The combined sodium carbonate layers were acidified with concentrated HCl and extracted with ethyl acetate. The combined ethyl acetate layers were dried over sodium sulfate, filtered, and evaporated to dryness in vacuo to give 2-methoxy-4-(1-acetyl-4-piperidyloxy)phenylacetic acid.

2-Methoxy-4-(1-acetyl-4-piperidyloxy)phenylacetic acid (35 mg, 0.11 mmol), 4-(2-methylphenyl)piperazine-2-carboxamide (25 mg, 0.11 mmol), EDC (28 mg, 0.15 mmol), and HBT (17 mg, 0.13 mmol) were combined in DMF (4 ml) under nitrogen. The mixture was rendered basic by addition of triethylamine (0.043 ml) and stirred at ambient temperature for 18 hours. The mixture was concentrated in vacuo and the residue was chromatographed on silica gel eluted with 2%

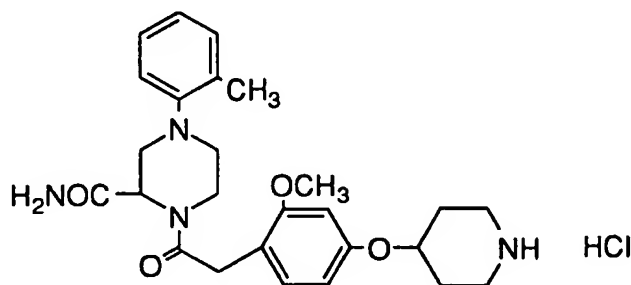
- 52 -

methanol in methylene chloride. The combined product fractions were evaporated to dryness in vacuo and the residue was rechromatographed on silica gel eluted with 96:4:0.4 methylene chloride:methanol:concentrated ammonia. The combined product fractions were evaporated to dryness in vacuo and the residue was concentrated from methanol and ether to give 1-(2-methoxy-4-(1-acetyl-4-piperidyloxy)phenylacetyl)-4-(2-methylphenyl)-piperazine-2-carboxamide.

¹H-NMR: Consistent with structure
TLC: silica gel, 5% methanol in methylene chloride: single component, R_f= 0.42
FABMS: M+H @ m/e= 509
HPLC: 92%
Anal. cal'd for C₂₈H₃₆N₄O₅·0.9 H₂O:
C, 64.07; H, 7.26; N, 10.68.
Found: C, 63.87; H, 7.00; N, 10.59.

EXAMPLE 10

1-(2-Methoxy-4-(4-piperidyloxy)phenylacetyl)-4-(2-methylphenyl)-piperazine-2-carboxamide dihydrochloride



2-Methoxy-4-(1-Boc-4-piperidyloxy)benzoic acid (3.2 g, 9.1 mmol) was dissolved in THF (35 ml). Thionyl chloride (1 ml, 1.63 g, 13.7 mmol) was added dropwise, followed by 2 drops of pyridine. The mixture was stirred at ambient temperature under nitrogen for 4.5 hours, then concentrated in vacuo. The residue was reconcentrated

- 53 -

from ether to give 2-methoxy-4-(1-Boc-4-piperidyloxy)benzoyl chloride.

5 A mixture of ether (66 ml) and 40% aqueous potassium hydroxide (20 ml) was cooled in ice. N-Nitrosomethylurea (6.6g) was added in portions with gentle swirling over 30 min. The ether layer was decanted and dried over solid potassium hydroxide for 15 min. The ether solution was decanted, and the decanted solution was cooled in an ice bath. A solution of 2-methoxy-4-(1-Boc-4-piperidyloxy)benzoyl chloride (3.26 g, 8.8 mmol) in THF (6 ml) was added dropwise and the mixture was stirred in the cold for 15 min and at ambient temperature for 3.5 hours. Nitrogen was passed through the mixture for 1 hour, and the solution was then concentrated in vacuo. A portion (930 mg) of the residue was dissolved in methanol and heated to reflux, and a solution of silver benzoate (200 mg) in triethylamine (2 ml) was added in five 0.1 ml portions at intervals of eight minutes. A sixth portion was added after an additional forty minutes' reflux, and after another five minutes, a seventh portion. After a final 30 minutes' reflux, the mixture was cooled and filtered, and the filtrate was concentrated in vacuo. The residue was chromatographed on silica gel eluted with 3%, followed by 5% methanol in methylene chloride. The product fractions were combined and evaporated to dryness in vacuo to give methyl 2-methoxy-4-(1-Boc-4-piperidyloxy)-phenylacetate.

25 Methyl 2-methoxy-4-(1-Boc-4-piperidyloxy)phenylacetate (1.37 g, 3.6 mmol) was dissolved in THF (27 ml) and treated with lithium hydroxide (4.5 ml of a 1 M aqueous solution, 4.5 mmol). The mixture was stirred at ambient temperature for 4.5 hours, then treated with an additional 0.9 ml of 1 M lithium hydroxide and stirred at ambient temperature for 18 hours. The mixture was concentrated in vacuo, and the residue was acidified with 1M HCl, and extracted with ethyl acetate. The combined ethyl acetate layers were dried over sodium sulfate, filtered, and evaporated to dryness in vacuo. The residue was reconcentrated from ether to give 2-methoxy-4-(1-Boc-4-piperidyloxy)phenylacetic acid.

- 54 -

2-Methoxy-4-(1-Boc-4-piperidyloxy)phenylacetic acid (331 mg, 0.91 mmol), 4-(2-methylphenyl)piperazine-2-carboxamide (200 mg, 0.91 mmol), EDC (209 mg, 1.09 mmol), and HBT (141 mg, 1.04 mmol) were combined in DMF (7 ml) under nitrogen. The mixture
5 was adjusted to pH ca. 9 (moistened E. Merck colorpHast indicator) by addition of triethylamine (0.4 ml) and stirred at ambient temperature for 72 hours. The mixture was concentrated in vacuo and the residue was partitioned between ethyl acetate and aqueous sodium bicarbonate. The ethyl acetate layer was washed with sodium bicarbonate and with
10 brine, dried over sodium sulfate, filtered, and evaporated to dryness in vacuo. The residue was chromatographed on silica gel eluted with 3% methanol in methylene chloride. The combined product fractions were evaporated to dryness in vacuo to give 1-(2-methoxy-4-(1-Boc-4-piperidyloxy)phenylacetyl)-4-(2-methylphenyl)piperazine-2-
15 carboxamide.

1-(2-methoxy-4-(1-Boc-4-piperidyloxy)phenylacetyl)-4-(2-methylphenyl)piperazine-2-carboxamide (423 mg, 0.75 mmol) was stirred in ethyl acetate (4 ml) in an ice bath under nitrogen. A cold, saturated solution (4 ml) of HCl in ethyl acetate was added and the
20 mixture stirred in the cold for 45 min. Nitrogen gas was passed through the mixture for 1 hour, and the reaction was concentrated in vacuo. The residue was reconcentrated from methanol and from ether to give 1-(2-methoxy-4-(4-piperidyloxy)phenylacetyl)-4-(2-methylphenyl)piperazine-2-carboxamide dihydrochloride.
25

¹H-NMR: Consistent with structure

TLC: silica gel, 90:10:1 methylene

chloride:methanol:concentrated ammonia:

single component, R_f= 0.23

30 FABMS: M+H @ m/e= 467 (free base)

HPLC: 100%

Anal. cal'd for C₂₆H₃₄N₄O₄•2.0HCl•0.4Et₂O•0.9 H₂O:

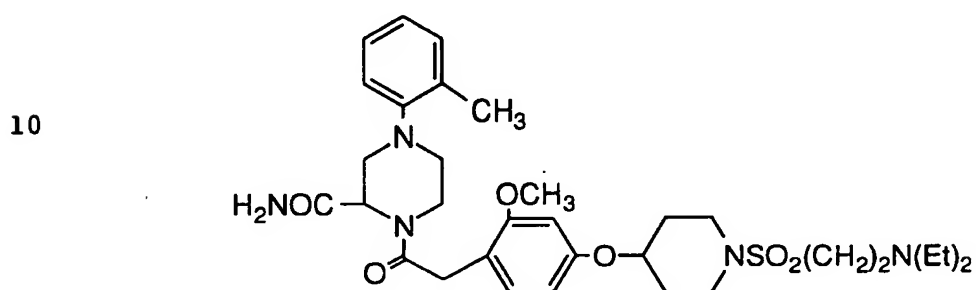
C, 56.63 H, 7.20 N, 9.57.

Found: C, 56.61; H, 7.22; N, 9.36.

- 55 -

EXAMPLE 11

5 1-(2-Methoxy-4-(1-(2-(N,N-Diethylamino)ethylsulfonyl)-4-piperidyloxy)phenylacetyl)-4-(2-methylphenyl)piperazine-2-carboxamide



15 2-Chloroethanesulfonyl chloride (0.035 ml, 54.6 mg, 0.33 mmol) in methylene chloride (3 ml) was cooled in an ice bath under nitrogen. A solution of 1-(2-methoxy-4-(4-piperidyloxy)phenylacetyl)-4-(2-methylphenyl)-piperazine-2-carboxamide dihydrochloride (149 mg, 0.28 mmol) and diisopropylethylamine (0.243 ml, 0.18 g, 1.4 mmol) in methylene chloride (3 ml) was added dropwise and the mixture was stirred in the cold for 18 hours. The mixture was concentrated in vacuo and the residue chromatographed on silica gel eluted with 3% methanol in methylene chloride. The combined product fractions were evaporated to dryness in vacuo to give 1-(2-methoxy-4-(1-ethenylsulfonyl-4-piperidyloxy)phenylacetyl)-4-(2-methylphenyl)piperazine-2-carboxamide.

25 1-(2-Methoxy-4-(1-ethenylsulfonyl-4-piperidyloxy)-phenylacetyl)-4-(2-methylphenyl)piperazine-2-carboxamide (52 mg, 0.093 mmol) was dissolved in methanol (5 ml), treated with diethylamine (0.013 ml, 9.2 mg, 0.12 mmol), and stirred at ambient temperature under nitrogen for 18 hours. An additional 0.01 ml of diethylamine was added and the mixture stirred another 24 hours at ambient temperature. The reaction was concentrated in vacuo and the residue was chromatographed on silica gel eluted with 3% followed by

30

- 56 -

5%, then 7% methanol in methylene chloride. The combined product fractions were evaporated to dryness in vacuo to give 1-(2-methoxy-4-(1-(2-(N,N-diethylamino)-ethylsulfonyl)-4-piperidyloxy)phenylacetyl)-4-(2-methylphenyl)piperazine-2-carboxamide: mp 70-140°C.

¹H-NMR: Consistent with structure

TLC: silica gel, 5% methanol in methylene chloride: single component, R_f= 0.30

FABMS: M+H @ m/e= 630

HPLC: 97%

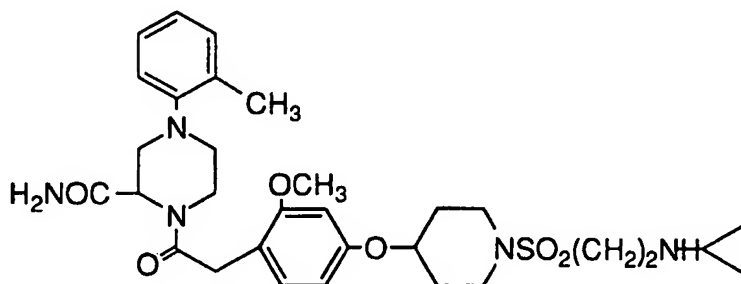
Anal. cal'd for C₃₂H₄₇N₅O₆S•0.25Et₂O•0.3 H₂O:

C, 60.62; H, 7.27; N, 10.71.

Found: C, 60.62; H, 7.49; N, 10.63.

EXAMPLE 12

1-(2-Methoxy-4-(1-(2-(N-cyclopropylamino)-ethylsulfonyl)-4-piperidyloxy)phenylacetyl)-4-(2-methylphenyl)piperazine-2-carboxamide



1-(2-Methoxy-4-(1-ethenylsulfonyl)-4-piperidyloxy)-phenylacetyl)-4-(2-methylphenyl)piperazine-2-carboxamide (69 mg, 0.12 mmol) was dissolved in methanol (4 ml), treated with cyclopropylamine (0.0072 ml, 10 mg, 0.18 mmol), and stirred at ambient temperature under nitrogen for 18 hours. An additional 0.014 ml of cyclopropylamine was added and the mixture stirred another 72 hours at ambient temperature. The reaction was concentrated in vacuo

- 57 -

and the residue was chromatographed on silica gel eluted with 4% methanol in methylene chloride. The combined product fractions were evaporated to dryness in vacuo. The residue was reconcentrated from ether to give 1-(2-methoxy-4-(1-(2-(N-cyclopropylamino)ethylsulfonyl)-4-piperidyloxy)phenylacetyl)-4-(2-methylphenyl)piperazine-2-carboxamide: mp 69-110°C.

¹H-NMR: Consistent with structure

TLC: silica gel, 5% methanol in methylene chloride: single component, R_f=0.35

FABMS: M+H @ m/e= 614

HPLC: 97%

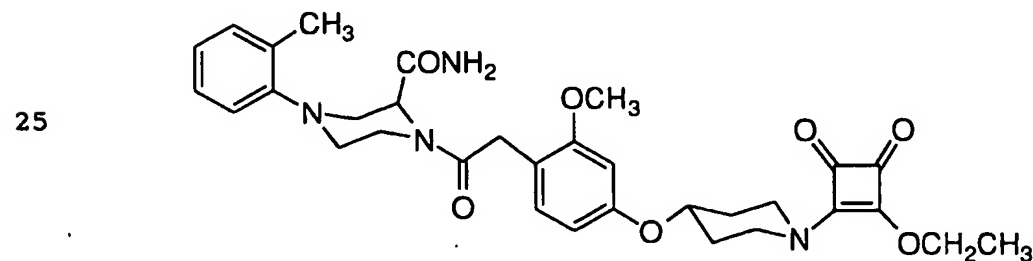
Anal. cal'd for C₃₁H₄₃N₅O₆S•0.4Et₂O•0.15 H₂O:

C, 60.59; H, 7.38; N, 10.84.

Found: C, 60.56; H, 7.26; N, 10.72.

EXAMPLE 13

1-(2-Methoxy-4-(1-(3-ethoxy-3-cyclobutene-1,2-dione-4-yl)-4-piperidyloxy)phenylacetyl)-4-(2-methylphenyl) piperazine-2-carboxamide



1-(2-Methoxy-4-(4-piperidyloxy)phenylacetyl)-4-(2-methylphenyl) piperazine-2-carboxamide (128 mg, 0.274 mmole) was dissolved in 4 ml of absolute ethanol. 3,4-Diethoxy-3-cyclobutene-1,2-dione (62 mg, 0.364 mmole), prepared according to the procedure in *Angew. Chem. Int. Ed.* **1966**, 5(10), 890, was then added to the solution and the resulting reaction mixture was heated to reflux for 72

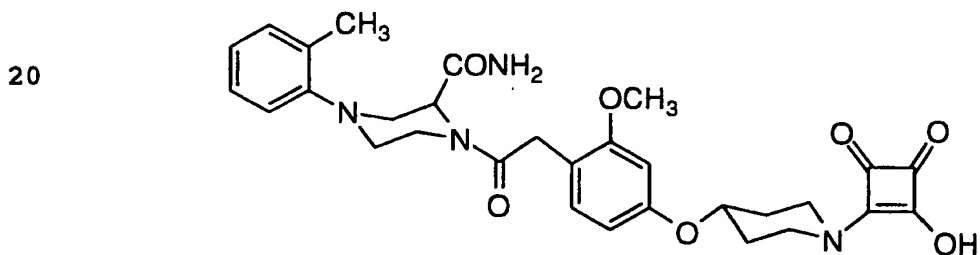
- 58 -

hr. The reaction mixture was cooled and filtered. The filter cake was washed with cold ethanol and dried to give the title compound as a white solid: m.p. 155-157°C.

- 5 ¹HNMR: Consistent with structure and confirms solvate;
TLC: R_f = 0.46 (9:1 chloroform-methanol), single component;
HPLC: >96% (214 nM);
FABMS: 591 (M⁺ + H);
10 Elemental Analysis calculated, for (C₃₂H₃₅N₃O₈•0.6 H₂O):
Calc'd: C, 64.00; H, 6.08; N, 7.00.
Found: C, 64.04; H, 5.98; N, 7.14.

EXAMPLE 14

- 15 1-(2-Methoxy-4-(1-(3-hydroxy-3-cyclobutene-1,2-dion-4-yl)-4-piperidyloxy)phenylacetyl)-4-(2-methylphenyl) piperazine-2-carboxamide



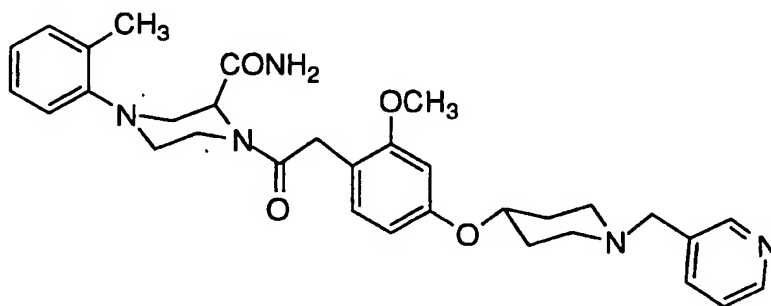
- 25 1-(2-Methoxy-4-(1-(3-ethoxy-3-cyclobutene-1,2-dion-4-yl)-4-piperidyloxy)phenylacetyl)-4-(2-methylphenyl)piperazine-2-carboxamide (87 mg, 0.147 mmole) was dissolved in 3 ml of ethanol, treated with one equivalent of 1N sodium hydroxide solution, and stirred at ambient temperature overnight. All volatiles were removed under reduced pressure and the residual material was applied directly to pre-coated silica gel plates (0.5mm thickness). Multiple elutions with a chloroform-methanol-acetic acid solvent mixture (80:20:2) afforded the title compound as a white solid: m.p. 144-148°C.
- 30

- 59 -

¹HNMR: Consistent with structure and confirms solvate;
TLC: R_f = 0.29 (80:20:2 chloroform-methanol-acetic acid);
HPLC: >97% (214 nm);
FABMS: 563 (M⁺ + H), 585 (M⁺ + Na);
5 Elemental Analysis, calculated for (C₃₀H₃₁N₃O₈•1.45CHCl₃):
Calc'd: C, 51.41; H, 4.45; N, 5.72.
Found: C, 51.57; H, 4.83; N, 5.55.

EXAMPLE 15

1-(2-Methoxy-4-(1-((pyrid-3-yl)methyl)-4-piperidyloxy)phenylacetyl)-
4-(2-methylphenyl) piperazine-2-carboxamide



1-(2-Methoxy-4-(4-piperidyloxy)phenylacetyl)-4-(2-methylphenyl) piperazine-2-carboxamide (110 mg, 0.236 mmole) was dissolved in 3 ml of dry N,N-dimethylformamide. To this solution was added 86 μ L (0.496 mmole) of diisopropylethylamine (DIEA) and 43 mg (0.26 mmole) of picolyl chloride. The reaction mixture was stirred at ambient temperature overnight and then was treated with an additional 20 mg of picolyl chloride. The pH of the reaction mixture was adjusted to 9 with DIEA and stirring was continued for 24 hr more.
All volatiles were removed under reduced pressure and the residual material was partitioned between ethyl acetate and water. The organic phase was washed with 5% sodium carbonate solution and brine, then dried and concentrated. The crude product mixture was purified via preparative thick layer chromatography on precoated silica gel plates

- 60 -

(80:20 chloroform-methanol elution) to give the title compound in homogeneous form: m.p. 78-81°C.

¹HNMR: Consistent with structure and confirms solvate;

5 TLC: R_f = 0.20 (90:10 chloroform-methanol);

HPLC: >98% (214 nM);

FABMS: 558 (M⁺ + H);

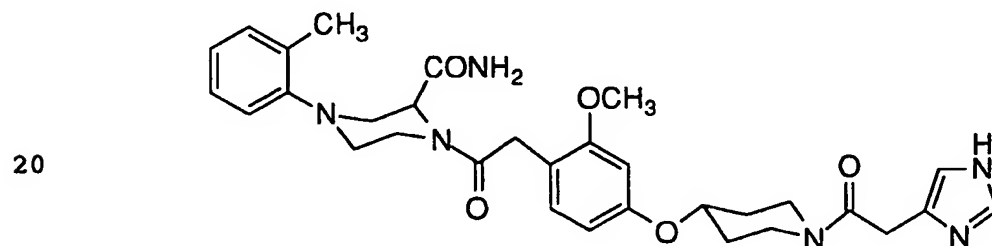
Elemental Analysis, calculated for (C₃₂H₃₉N₅O₄•0.75CHCl₃):

Calc'd: C, 60.77; H, 6.19; N, 10.82.

10 Found: C, 60.99; H, 6.34; N, 10.84.

EXAMPLE 16

15 1-(2-Methoxy-4-(1-((imidazol-4-yl)methylcarbonyl)-4-piperidyloxy)-phenylacetyl)-4-(2-methylphenyl) piperazine-2-carboxamide



25 1-(2-Methoxy-4-(4-piperidyloxy)phenylacetyl)-4-(2-methylphenyl) piperazine-2-carboxamide (200 mg, 0.429 mmole) and 4-imidazoleacetic acid (70 mg, 0.429 mmole) were dissolved in 4 ml of dry N,N-dimethylformamide at room temperature. To this solution was added 209 mg (0.472 mmole) of benzotriazol-1-yloxy-tris(dimethylamino)-phosphonium hexafluorophosphate (BOP). The pH of the reaction mixture was adjusted to 9 with the addition of diisopropylethylamine (DIEA) in 100 µL increments. The reaction mixture was stirred at ambient temperature for 2 hr whereupon all volatiles were removed under reduced pressure. The residue was suspended in ethyl acetate and this suspension was washed with water. The organic phase and some insoluble material were combined,

30

- 61 -

concentrated, and azeotropically dried with toluene. The resulting semi-solid was purified via preparative thick layer chromatography on precoated silica gel plates (85:15:1.5 chloroform-methanol-concentrated ammonium hydroxide elution) to give the title compound in homogeneous form: m.p. 120-124°C.

¹HNMR: Consistent with structure and confirms solvate;

TLC: R_f = 0.50 (80:20:2 chloroform-methanol-conc.

ammonium hydroxide);

HPLC: >95% (214 nM);

FABMS: 575 (M⁺ + H);

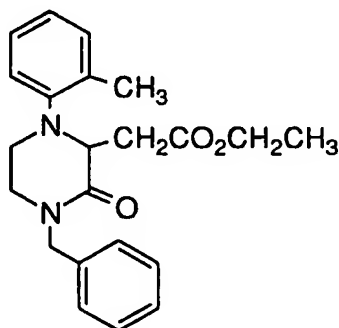
Elemental Analysis, calculated for (C₃₁H₃₈N₆O₅•1.25CHCl₃):

Calc'd: C, 53.50; H, 5.47; N, 11.61.

Found: C, 53.42; H, 5.70; N, 11.43.

EXAMPLE 17

1-Benzyl-3-Ethoxycarbonylmethyl-4-(2-methylphenyl)piperazin-2-one



Step 1: N-Benzyl-N-(2-(2-methylphenylamino)ethyl-3-(ethoxycarbonyl)acrylamide

To a stirred solution of N-benzyl-N'-(2-methylphenyl)-1,2-diaminoethane hydrochloride (10 g; 0.036 mol; prepared by the method given in Example 5), ethyl fumarate (5.7 g; 0.040 mol), and EDC (8.3 g; 0.043 mol) in DMF (200 mL) was added DIEA (13.8 mL; 0.0792 mol) dropwise over a period of 30 minutes. The resulting mixture was

- 62 -

stirred at ambient temperature for 18 h. The solvent was removed under reduced pressure and the residue was partitioned between EtOAc and saturated aqueous NaHCO₃. The organic phase was separated and washed with 5% aqueous citric acid, saturated aqueous NaHCO₃, and brine. The organic phase was dried (MgSO₄), filtered and evaporated under reduced pressure. The residue was purified by pressurized silica gel column chromatography using 1:3 EtOAc:hexanes as eluant. The title compound was obtained as a yellow oil (HPLC retention time 9.60 min).

1-Benzyl-3-Ethoxycarbonylmethyl-4-(2-methylphenyl)-piperazin-2-one N-Benzyl-N-(2-(2-methylphenylamino)ethyl-3-(ethoxycarbonyl)acrylamide (10 g, 0.027 mol) was refluxed in 10:1 EtOH:HOAc (150 mL) for 24 h to give a 3:5 mixture of two products, HPLC retention times 8.47 min and 11.0 min, and TLC R_f values of 0.33 and 0.20 (1:3 EtOAc:hexanes), respectively. The solvents were removed under reduced pressure and the residue was purified by pressurized silica gel column chromatography using a gradient elution of 20-30% EtOAc:hexanes. The title compound (higher TLC R_f, longer HPLC retention time, major product) was obtained as a colorless oil.

¹H-NMR: Consistent with structure

TLC: silica gel, 1:3 EtOAc:hexanes:
single component, R_f= 0.33

FABMS: M+H @ m/e= 367

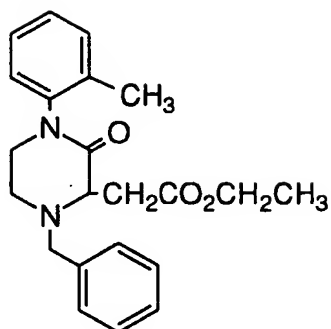
HPLC: retention time 11.0 min; >99%

EXAMPLE 18

1-Benzyl-2-Ethoxycarbonylmethyl-4-(2-methylphenyl)piperazin-3-one

- 63 -

5



10

The slower eluting isomer from the chromatographic separation in Step 2 of Example 17 was isolated. The title compound (lower TLC R_f, shorter HPLC retention time, minor product from Step 2 of Example 17) was obtained as a colorless oil.

15

¹H-NMR: Consistent with structure
TLC: silica gel, 1:3 EtOAc:hexanes:
single component, R_f= 0.20
FABMS: M+H @ m/e= 367
HPLC: retention time 8.47 min; >99%

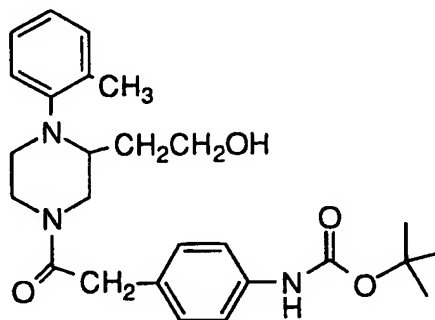
20

EXAMPLE 19

25

1-(4-(t-Butyloxycarbonylamino)phenylacetyl)-3-(2-hydroxyethyl)-4-(2-methylphenyl)piperazine

30



Step 1:

1-Benzyl-3-(2-hydroxyethyl)-4-(2-methylphenyl)piperazine

- 64 -

1-Benzyl-3-ethoxycarbonylmethyl-4-(2-methylphenyl)-
piperazin-2-one from Example 17 (2.5 g; 6.8 mmol) in dry THF (25
mL) was added dropwise to a stirred, 0°C solution of LAH in THF (27
mL of a 1.0 M solution; 27 mmol). The reaction was stirred at 0°C for
5 1 h and then at ambient temperature for 18 h. The reaction was diluted
with ether (50 mL), cooled to 0°C, and then quenched by the slow
dropwise addition of 5 N aqueous NaOH. The resulting suspension was
stirred at ambient temperature for 1 h and filtered through Celite. The
10 filtercake was washed with 1:1 THF:EtOAc. The filtrate solvents were
evaporated under reduced pressure and the residue was purified by
pressurized silica gel column chromatography using a gradient elution
of 1-4% MeOH:CH₂Cl₂. The title compound was obtained as an oil
(¹H-NMR: consistent with structure; TLC: silica gel, 4%
MeOH:CH₂Cl₂: single component, R_f= 0.45; FABMS: M+H @ m/e=
15 311; HPLC: 99%, retention time 9.81 min).

Step 2: 3-(2-Hydroxyethyl)-4-(2-methylphenyl)piperazine
1-Benzyl-3-(2-hydroxyethyl)-4-(2-methylphenyl)piperazine
from Step 1 above (1.5 g; 4.8 mmol) in 50 mL of MeOH containing 150
20 mg of palladium black was shaken on a Parr apparatus under an
atmosphere of hydrogen (55 psig) for 18 h. The catalyst was removed
by filtration through Celite and the filtercake was washed with MeOH.
The filtrate solvents were evaporated under reduced pressure to give the
title compound as an oil (¹H-NMR: consistent with structure; FABMS:
25 M+H @ m/e= 221; HPLC: 97%, retention time 5.20 min).

Step 3: 1-(4-(t-Butyloxycarbonylamino)phenylacetyl)-3-(2-
hydroxyethyl)-4-(2-methylphenyl)piperazine
To a stirred solution of 3-(2-hydroxyethyl)-4-(2-
30 methylphenyl)piperazine from Step 2 above (0.300 g; 1.36 mmol), 4-(t-
butyloxycarbonylamino)phenylacetic acid (0.342 g; 1.50 mmol), HOBT
(0.18 g; 1.5 mmol), and EDC (0.315 g; 1.64 mmol) in DMF (30 mL)
was added DIEA (0.29 mL; 1.7 mmol). The reaction was stirred at
ambient temperature for 18 h and the solvent was evaporated under

- 65 -

reduced pressure. The residue was partitioned between EtOAc and saturated aqueous NaHCO₃. The organic phase was separated and washed with saturated aqueous NaHCO₃ and brine. The organic phase was dried (MgSO₄), filtered, and the solvent was evaporated under reduced pressure. The residue was purified by pressurized silica gel column chromatography using 2:1 EtOAc:hexanes as eluant. Evaporation of a CH₂Cl₂ solution of the title compound under reduced pressure gave an amorphous solid.

¹H-NMR: Consistent with structure

TLC: silica gel, 3:1 EtOAc:hexanes:
single component, R_f= 0.40

FABMS: M+H @ m/e= 454

HPLC: >99%, retention time 9.08 min

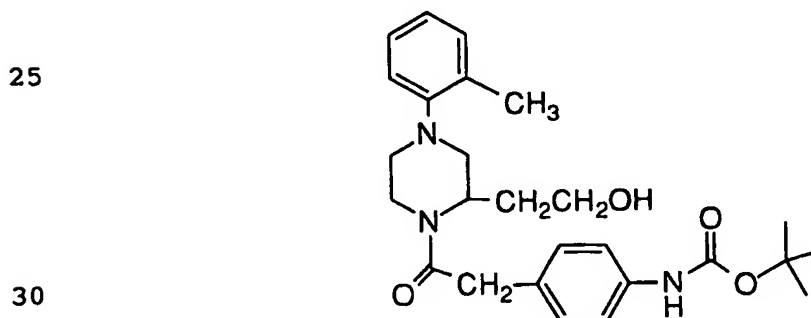
Anal. cal'd for C₂₆H₃₅N₃O₄•0.4 H₂O:

C, 67.77; H, 7.83; N, 9.19

Found: C, 67.61; H, 7.64; N, 9.14

EXAMPLE 20

1-(4-(t-Butyloxycarbonylamino)phenylacetyl)-2-(2-hydroxyethyl)-4-(2-methylphenyl)piperazine



Step 1: 1-Benzyl-2-(2-hydroxyethyl)-4-(2-methylphenyl)piperazine
1-Benzyl-2-ethoxycarbonylmethyl-4-(2-methylphenyl)-
piperazin-8-one from Example 18 (5.0 g; 14 mmol) in dry THF (50
mL) was added dropwise to a stirred, 0°C solution of LAH in THF (56

- 66 -

mL of a 1.0 M solution; 56 mmol). The reaction was stirred at 0°C for 1 h and then at ambient temperature for 18 h. The reaction was diluted with ether (100 mL), cooled to 0°C, and then quenched by the slow dropwise addition of 5 N aqueous NaOH. The resulting suspension was stirred at ambient temperature for 1 h and filtered through Celite. The filtercake was washed with 1:1 THF:EtOAc. The filtrate solvents were evaporated under reduced pressure and the residue was purified by pressurized silica gel column chromatography using a gradient elution of 1-4% MeOH:CH₂Cl₂. The title compound was obtained as an oil (¹H-NMR: consistent with structure; TLC: silica gel, 3% MeOH:CH₂Cl₂: single component, R_f = 0.42; FABMS: M+H @ m/e = 311; HPLC: 99%, retention time 9.98 min).

Step 2: 2-(2-Hydroxyethyl)-4-(2-methylphenyl)piperazine
1-Benzyl-2-(2-hydroxyethyl)-4-(2-methylphenyl)piperazine from Step 1 above (3.2 g; 10 mmol) in 50 mL of MeOH containing 150 mg of palladium black was shaken on a Parr apparatus under an atmosphere of hydrogen (55 psig) for 18 h. The catalyst was removed by filtration through Celite and the filtercake was washed with MeOH. The filtrate solvents were evaporated under reduced pressure to give the title compound as an oil (¹H-NMR: consistent with structure; FABMS: M+H @ m/e = 221; HPLC: 98%, retention time 5.38 min).

Step 3: 1-(4-(t-Butyloxycarbonylamino)phenylacetyl)-2-(2-hydroxyethyl)-4-(2-methylphenyl)piperazine
To a stirred solution of 2-(2-hydroxyethyl)-4-(2-methylphenyl)piperazine from Step 2 above (0.40 g; 1.82 mmol), 4-(t-butyloxycarbonylamino)phenylacetic acid (0.502 g; 2.00 mmol), HOBT (0.27 g; 2.0 mmol), and EDC (0.419 g; 2.18 mmol) in DMF (40 mL) was added DIEA (0.44 mL; 2.5 mmol). The reaction was stirred at ambient temperature for 18 h and the solvent was evaporated under reduced pressure. The residue was partitioned between EtOAc and saturated aqueous NaHCO₃. The organic phase was separated and washed with saturated aqueous NaHCO₃ and brine. The organic phase

- 67 -

was dried (MgSO₄), filtered, and the solvent was evaporated under reduced pressure. The residue was purified by pressurized silica gel column chromatography using 2:1 EtOAc:hexanes as eluant. Evaporation of a CH₂Cl₂ solution of the title compound under reduced pressure gave an amorphous solid.

¹H-NMR: Consistent with structure

TLC: silica gel, 1:1 EtOAc:hexanes:
single component, R_f = 0.16

FABMS: M+H @ m/e = 454

HPLC: 99%, retention time 9.99 min

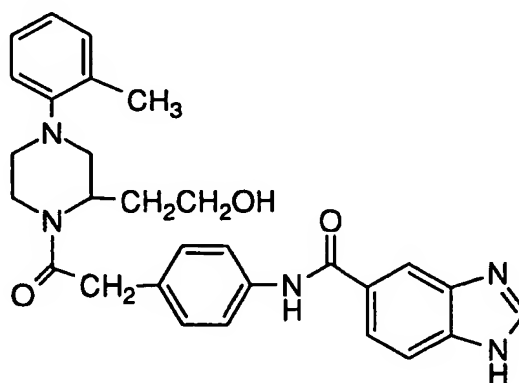
Anal. cal'd for C₂₆H₃₅N₃O₄•0.8 H₂O:

C, 66.73; H, 7.88; N, 8.98

Found: C, 66.76; H, 7.59; N, 9.97

EXAMPLE 21

1-(4-(5-Benzimidazolylcarbonylamino)phenylacetyl)-2-(2-hydroxyethyl)-4-(2-methylphenyl)piperazine



To a stirred solution of 2-(2-hydroxyethyl)-4-(2-methylphenyl)piperazine from Step 2 of Example 20 (0.20 g; 0.91 mmol), 4-(5-benzimidazolylcarbonylamino)phenylacetic acid (0.299 g; 1.00 mmol), HOBt (0.14 g; 1.0 mmol), and EDC (0.210 g; 1.09 mmol) in DMF (30 mL) was added DIEA (0.23 mL; 1.3 mmol). The reaction

- 68 -

was stirred at ambient temperature for 18 h and the solvent was evaporated under reduced pressure. The residue was partitioned between CH₂Cl₂ and saturated aqueous NaHCO₃. The organic phase was separated and washed with saturated aqueous NaHCO₃ and brine. The organic phase was dried (MgSO₄), filtered, and the solvent was evaporated under reduced pressure. The residue was purified by pressurized silica gel column chromatography using 95:5:0.5 CH₂Cl₂:MeOH:NH₄OH as eluant. Trituration in EtOAc gave the title compound as an amorphous solid.

¹H-NMR: Consistent with structure

TLC: silica gel, 92:8:0.4 CH₂Cl₂:MeOH:NH₄OH:
single component, R_f = 0.35

FABMS: M+H @ m/e = 498

HPLC: 99%, retention time 7.25 min

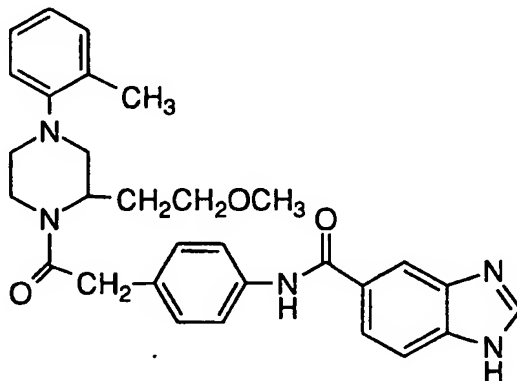
Anal. cal'd for C₂₉H₃₁N₅O₃•1.0 H₂O•0.09 EtOAc:

C, 67.36; H, 6.49; N, 13.38

Found: C, 67.52; H, 6.51; N, 13.38

EXAMPLE 22

1-(4-(5-Benzimidazolylcarbonylamino)phenylacetyl)-2-(2-methoxyethyl)-4-(2-methylphenyl)piperazine



- 69 -

Step 1: 1-t-Butyloxycarbonyl-2-(2-hydroxyethyl)-4-(2-methylphenyl)piperazine

To a stirred solution of 2-(2-hydroxyethyl)-4-(2-methylphenyl)piperazine from Step 2 of Example 20 (2.0 g; 9.1 mmol) in DMF (50 mL) was added di-t-butyl dicarbonate (2.1 g; 9.6 mmol). The reaction was stirred at ambient temperature for 18 h and the solvent was evaporated under reduced pressure. The residue was purified by pressurized silica gel column chromatography using 1:4 EtOAc:hexanes as eluant. The title compound was obtained as a gum (¹H-NMR: consistent with structure; TLC: silica gel, 1:3 EtOAc:hexanes: single component, R_f= 0.33; FABMS: M+H @ m/e= 321; HPLC: >99%, retention time 9.88 min).

Step 2: 1-t-Butyloxycarbonyl-2-(2-methoxyethyl)-4-(2-methylphenyl)-piperazine

To a stirred, 0°C solution of 1-t-butyloxycarbonyl-2-(2-hydroxyethyl)-4-(2-methylphenyl)piperazine from Step 1 above (0.38 g; 1.2 mmol) and iodomethane (0.20 mL; 3.4 mmol) in dry THF (20 mL) was added NaH (60 mg of a 60% suspension in mineral oil; 1.5 mmol). The reaction was stirred at 0°C for 15 min and then at ambient temperature for 18 h. The reaction was quenched by adding several drops of MeOH and the solvents were evaporated under reduced pressure. The residue was partitioned between EtOAc and water. The organic phase was separated and washed with water and brine. The organic phase was dried (MgSO₄), filtered, and the solvent was removed under reduced pressure. The residue was purified by pressurized silica gel column chromatography using 1:4 EtOAc:hexanes as eluant. The title compound was obtained as a gum (¹H-NMR: consistent with structure; TLC: silica gel, 1:3 EtOAc:hexanes: single component, R_f= 0.62; FABMS: M+H @ m/e= 335; HPLC: >99%, retention time 11.7 min).

Step 3: 2-(2-methoxyethyl)-4-(2-methylphenyl)piperazine
hydrochloride

- 70 -

Through a stirred, 0°C solution of 1-t-butyloxycarbonyl-2-(2-methoxyethyl)-4-(2-methylphenyl)piperazine from Step 2 above (0.350 g; 1.05 mmol) in dry EtOAc (40 mL) was bubbled HCl gas for 20 min. The reaction was stirred at 0°C for 15 min and then at ambient temperature for 30 min. The solvent was evaporated under reduced pressure to give the title compound as an amorphous solid (¹H-NMR: consistent with structure; HPLC: >99%, retention time 6.18 min).

Step 4: 1-(4-(5-Benzimidazolylcarbonylamino)phenylacetyl)-2-(2-methoxyethyl)-4-(2-methylphenyl)piperazine

To a stirred solution of 2-(2-methoxyethyl)-4-(2-methylphenyl)piperazine hydrochloride from Step 3 above (0.25 g, 0.92 mmol), 4-(5-benzimidazolylcarbonylamino)phenylacetic acid (0.299 g; 1.00 mmol), HOBt (0.14 g; 1.0 mmol), and EDC (0.210 g; 1.09 mmol) in DMF (30 mL) was added DIEA (0.23 mL; 1.3 mmol). The reaction was stirred at ambient temperature for 18 h and the solvent was evaporated under reduced pressure. The residue was partitioned between CH₂Cl₂ and saturated aqueous NaHCO₃. The organic phase was separated and washed with saturated aqueous NaHCO₃ and brine. The organic phase was dried (MgSO₄), filtered, and the solvent was evaporated under reduced pressure. The residue was purified by pressurized silica gel column chromatography using 95:5:0.5 CH₂Cl₂:MeOH:NH₄OH as eluant. Evaporation of a CH₂Cl₂ solution of the title compound under reduced pressure gave an amorphous solid.

¹H-NMR: Consistent with structure

TLC: silica gel, 93:7:0.35 CH₂Cl₂:MeOH:NH₄OH:

single component, R_f = 0.26

FABMS: M+H @ m/e = 512

HPLC: 98.7%, retention time 8.04 min

Anal. cal'd for C₃₀H₃₃N₅O₃•1.0 H₂O:

C, 68.03; H, 6.66; N, 13.22

Found: C, 68.05; H, 6.77; N, 13.17

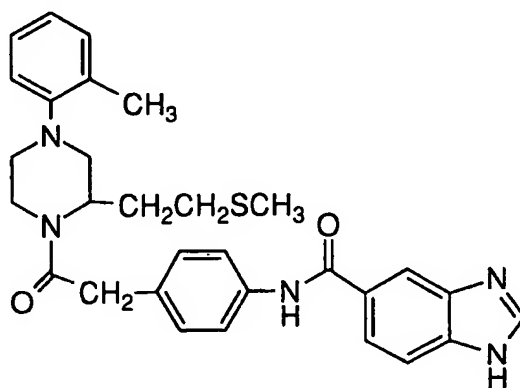
- 71 -

EXAMPLE 23

1-(4-(5-Benzimidazolylcarbonylamino)phenylacetyl)-2-(2-methylthioethyl)-4-(2-methylphenyl)piperazine

5

10



15

Step 1: 1-t-Butyloxycarbonyl-2-(2-methylsulfonyloxyethyl)-4-(2-methylphenyl)piperazine

20

To a stirred, 0°C solution of 1-t-butyloxycarbonyl-2-(2-hydroxyethyl)-4-(2-methylphenyl)piperazine from Step 1 of Example 22 (0.32 g; 1.0 mmol) and DIEA (0.35 mL; 2.0 mmol) in dry CH₂Cl₂ (10 mL) was added methanesulfonyl chloride (0.085 mL; 1.1 mmol). The reaction was stirred at 0°C for 15 min and then at ambient temperature for 5 h. The solvent was evaporated under reduced pressure and the residue was partitioned between EtOAc and water. The organic phase was separated and washed with water and brine. The organic phase was dried (MgSO₄), filtered, the solvent was removed under reduced pressure and the title compound, obtained as a gum, was used directly in the next step.

25

30

Step 2: 1-t-Butyloxycarbonyl-2-(2-methylthioethyl)-4-(2-methylphenyl)piperazine

A stirred solution of 1-t-butyloxycarbonyl-2-(2-methylsulfonyloxyethyl)-4-(2-methylphenyl)piperazine from Step 1 above (0.39 g; 0.98 mmol) and sodium thiomethoxide (0.21 g; 3.0 mmol) in dry THF (15 mL) was heated to reflux for 18 h. The solvent

- 72 -

was evaporated under reduced pressure and the residue was partitioned between EtOAc and water. The organic phase was separated and washed with saturated aqueous NaHCO₃ and brine. The organic layer was dried (MgSO₄), filtered, and the solvent was evaporated under reduced pressure. The residue was purified by pressurized silica gel column chromatography using 1:4 EtOAc:hexanes as eluant. The title compound was isolated as a gum (¹H-NMR: consistent with structure; TLC: silica gel, 1:4 EtOAc:hexanes: single component, R_f= 0.50; FABMS: M+H @ m/e= 351; HPLC: >99%, retention time 12.0 min).

Step 3: 2-(2-Methylthioethyl)-4-(2-methylphenyl)piperazine hydrochloride

Through a stirred, 0°C solution of 1-t-butyloxycarbonyl-2-(2-methylthioethyl)-4-(2-methylphenyl)piperazine from Step 2 above (0.30 g; 0.86 mmol) in dry EtOAc (40 mL) was bubbled HCl gas for 20 min. The reaction was stirred at 0°C for 15 min and then at ambient temperature for 30 min. The solvent was evaporated under reduced pressure to give the title compound as an amorphous solid (¹H-NMR: consistent with structure; HPLC: >99%, retention time 6.39 min).

Step 4: 1-(4-(5-Benzimidazolylcarbonylamino)phenylacetyl)-2-(2-methylthioethyl)-4-(2-methylphenyl)piperazine

To a stirred solution of 2-(2-methylthioethyl)-4-(2-methylphenyl)piperazine hydrochloride from Step 3 above (0.25 g, 0.87 mmol), 4-(5-benzimidazolylcarbonylamino)phenylacetic acid (0.282 g; 0.96 mmol), HOBT (0.14 g; 1.0 mmol), and EDC (0.192 g; 1.00 mmol) in DMF (30 mL) was added DIEA (0.21 mL; 1.2 mmol). The reaction was stirred at ambient temperature for 18 h and the solvent was evaporated under reduced pressure. The residue was partitioned between CH₂Cl₂ and saturated aqueous NaHCO₃. The organic phase was separated and washed with saturated aqueous NaHCO₃ and brine. The organic phase was dried (MgSO₄), filtered, and the solvent was evaporated under reduced pressure. The residue was purified by pressurized silica gel column chromatography using 95:5:0.5

- 73 -

CH₂Cl₂:MeOH:NH₄OH as eluant. Evaporation of a CH₂Cl₂ solution of the title compound under reduced pressure gave an amorphous solid.

¹H-NMR: Consistent with structure

5 TLC: silica gel, 90:10:0.5 CH₂Cl₂:MeOH:NH₄OH:
single component, R_f = 0.47

FABMS: M+H @ m/e = 528

HPLC: 97%, retention time 8.42 min

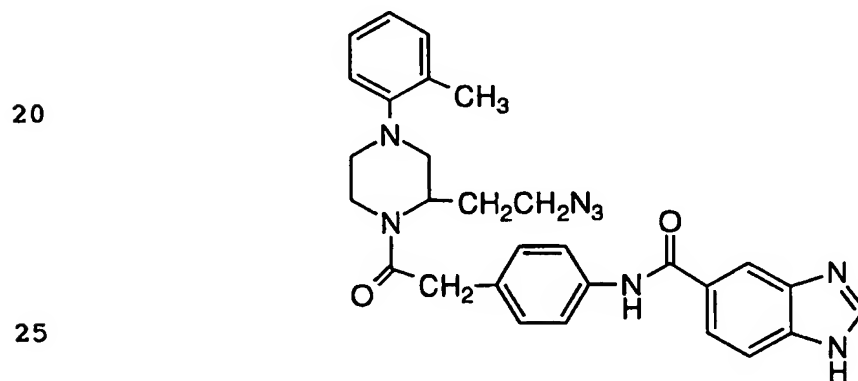
10 Anal. cal'd for C₃₀H₃₃N₅O₂S•1.5 H₂O:

C, 64.96; H, 6.54; N, 12.63

Found: C, 65.01; H, 6.16; N, 12.36

EXAMPLE 24

15 1-(4-(5-Benzimidazolylcarbonylamino)phenylacetyl)-2-(2-azidoethyl)-4-(2-methylphenyl)piperazine



Step 1: 1-t-Butyloxycarbonyl-2-(2-azidoethyl)-4-(2-methylphenyl)piperazine

30 A stirred solution of 1-t-butyloxycarbonyl-2-(2-methylsulfonyloxyethyl)-4-(2-methylphenyl)piperazine from Step 1 of Example 23 (0.40 g; 1.0 mmol) and sodium azide (0.30 g; 4.6 mmol) in dry DMF (15 mL) was heated to 60°C for 18 h. The solvent was evaporated under reduced pressure and the residue was partitioned between EtOAc and water. The organic phase was separated and

- 74 -

washed with saturated aqueous NaHCO₃ and brine. The organic layer was dried (MgSO₄), filtered, and the solvent was evaporated under reduced pressure. The residue was purified by pressurized silica gel column chromatography using 1:9 EtOAc:hexanes as eluant. The title compound was isolated as a gum (¹H-NMR: consistent with structure; TLC: silica gel, 1:9 EtOAc:hexanes: single component, R_f= 0.50; FABMS: M+H @ m/e= 346; HPLC: >99%, retention time 12.4 min).

Step 2: 2-(2-Azidoethyl)-4-(2-methylphenyl)piperazine hydrochloride

Through a stirred, 0°C solution of 1-t-butyloxycarbonyl-2-(2-azidoethyl)-4-(2-methylphenyl)piperazine from Step 1 above (0.29 g; 0.84 mmol) in dry EtOAc (40 mL) was bubbled HCl gas for 20 min. The reaction was stirred at 0°C for 15 min and then at ambient temperature for 30 min. The solvent was evaporated under reduced pressure to give the title compound as an amorphous solid (¹H-NMR: consistent with structure; HPLC: >99%, retention time 6.43 min).

Step 3: 1-(4-(5-Benzimidazolylcarbonylamino)phenylacetyl)-2-(2-azidoethyl)-4-(2-methylphenyl)piperazine

To a stirred solution of 2-(2-azidoethyl)-4-(2-methylphenyl)-piperazine hydrochloride from Step 3 above (0.24 g, 0.85 mmol), 4-(5-benzimidazolylcarbonylamino)phenylacetic acid (0.277 g; 0.94 mmol), HOBt (0.14 g; 1.0 mmol), and EDC (0.192 g; 1.00 mmol) in DMF (30 mL) was added DIEA (0.21 mL; 1.2 mmol). The reaction was stirred at ambient temperature for 18 h and the solvent was evaporated under reduced pressure. The residue was partitioned between CH₂Cl₂ and saturated aqueous NaHCO₃. The organic phase was separated and washed with saturated aqueous NaHCO₃ and brine. The organic phase was dried (MgSO₄), filtered, and the solvent was evaporated under reduced pressure. The residue was purified by pressurized silica gel column chromatography using 95:5:0.5 CH₂Cl₂:MeOH:NH₄OH as eluant. Evaporation of a CH₂Cl₂

- 75 -

solution of the title compound under reduced pressure gave an amorphous solid.

¹H-NMR: Consistent with structure

5 TLC: silica gel, 90:10:0.5 CH₂Cl₂:MeOH:NH₄OH:
single component, R_f= 0.54

FABMS: M+H @ m/e= 523

HPLC: >99%, retention time 8.38 min

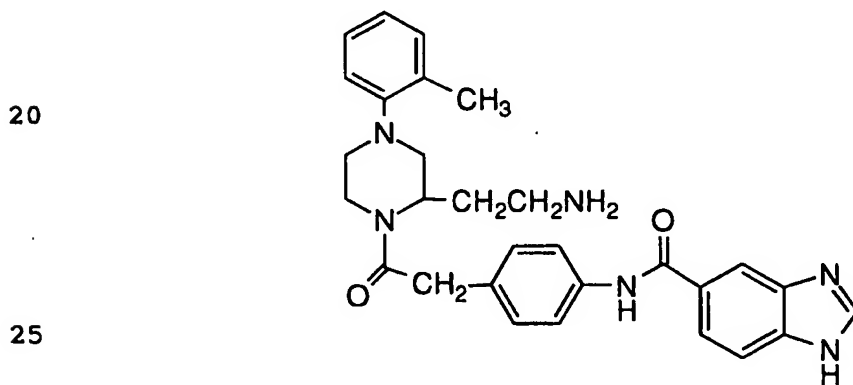
Anal. cal'd for C₂₉H₃₀N₈O₂•0.33 CH₂Cl₂:

10 C, 63.98; H, 5.61; N, 20.35

Found: C, 63.85; H, 5.65; N, 20.31

EXAMPLE 25

15 1-(4-(5-Benzimidazolylcarbonylamino)phenylacetyl)-2-(2-aminoethyl)-
4-(2-methylphenyl)piperazine



A solution of 1-(4-(5-benzimidazolylcarbonylamino)-phenylacetyl)-2-(2-aminoethyl)-4-(2-methylphenyl)piperazine from
30 Example 24 (0.24 g, 0.46 mmol) and triphenylphosphine (0.235 g; 0.90 mmol) in 10:1 THF:H₂O was stirred at ambient temperature for 48 h. The solvents were removed under reduced pressure and the residue was partitioned between EtOAc and brine. The organic phase was dried (MgSO₄), filtered, and the solvent was evaporated under reduced pressure. The residue was purified by preparative reverse phase HPLC

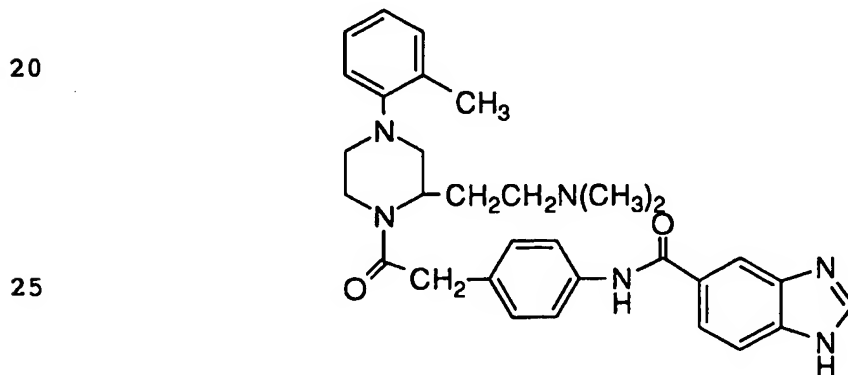
- 76 -

using an H₂O:CH₃CN gradient containing 0.1% TFA. The TFA salt of the title compound was obtained as an amorphous powder by lyophilization.

- 5 ¹H-NMR: Consistent with structure
TLC: silica gel, 90:10:0.5 CH₂Cl₂:MeOH:NH₄OH:
single component, R_f = 0.14
FABMS: M+H @ m/e = 497
HPLC: >99%, retention time 6.09 min
10 Anal. cal'd for C₂₉H₃₂N₆O₂•2.45 TFA•0.55 H₂O:
C, 51.81; H, 4.56; N, 10.69
Found: C, 51.80; H, 4.55; N, 11.00

EXAMPLE 26

15 1-(4-(5-Benzimidazolylcarbonylamino)phenylacetyl)-2-(2-dimethyl-aminoethyl-4-(2-methylphenyl)piperazine



- To a stirred solution of 1-(4-(5-benzimidazolylcarbonyl-
amino)-phenylacetyl)-2-(2-aminoethyl-4-(2-methylphenyl)piperazine
30 TFA salt from Example 25 (0.10 g, 0.20 mmol) and 37% aqueous
formaldehyde (0.10 mL; 1.2 mmol) in 100:1 MeOH:HOAc (10 mL) was
added NaCNBH₃ (76 mg; 1.2 mmol). The reaction was stirred at
ambient temperature for 18 h. The solvents were removed under
reduced pressure and the residue was partitioned between EtOAc and

- 77 -

saturated aqueous NaHCO₃. The organic phase was dried (MgSO₄), filtered, and the solvent was evaporated under reduced pressure. The residue was purified by preparative reverse phase HPLC using an H₂O:CH₃CN gradient containing 0.1% TFA. The TFA salt of the title compound was obtained as an amorphous powder by lyophilization.

¹H-NMR: Consistent with structure

TLC: silica gel, 90:10:0.5 CH₂Cl₂:MeOH:NH₄OH:

single component, R_f = 0.19

FABMS: M+H @ m/e = 525

HPLC: 95%, retention time 6.39 min

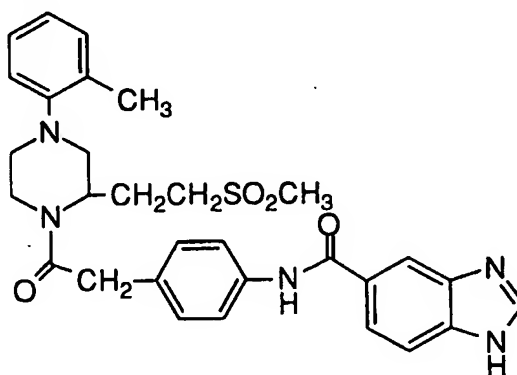
Anal. cal'd for C₃₁H₃₆N₆O₂•1.8 TFA•1.5 H₂O:

C, 54.90; H, 5.43; N, 11.10

Found: C, 54.93; H, 5.47; N, 10.90

EXAMPLE 27

1-(4-(5-Benzimidazolylcarbonylamino)phenylacetyl)-2-(2-methylsulfonyl-ethyl-4-(2-methylphenyl)piperazine



A solution of 1-(4-(5-benzimidazolylcarbonylamino)-phenylacetyl)-2-(2-methylthioethyl)-4-(2-methylphenyl)piperazine from Example 23 (0.10 g, 0.19 mmol), N-methylmorpholine-N-oxide (110 mg; 0.95 mmol) and OsO₄ (0.20 mL of a 4 wt. % solution in water; 0.031 mmol) in 10:1 acetone:water (5 mL) was stirred at ambient

- 78 -

temperature for 72 h. The solvents were removed under reduced pressure and the residue was purified by preparative reverse phase HPLC using an H₂O:CH₃CN gradient containing 0.1% TFA. The TFA salt of the title compound was obtained as an amorphous powder by lyophilization.

¹H-NMR: Consistent with structure

TLC: silica gel, 95:5:0.5 CH₂Cl₂:MeOH:NH₄OH:

single component, R_f = 0.13

FABMS: M+H @ m/e = 560

HPLC: 98%, retention time 7.18 min

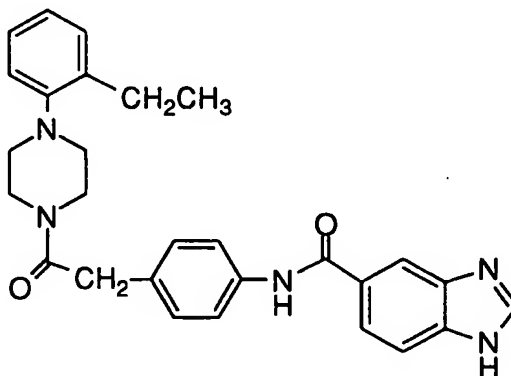
Anal. cal'd for C₃₀H₃₈N₅O₄S•1.55 TFA•1.4 H₂O:

C, 52.19; H, 4.94; N, 9.20

Found: C, 52.20; H, 4.64; N, 9.59

EXAMPLE 28

1-(4-(5-Benzimidazolylcarbonylamino)phenylacetyl)-4-(2-ethylphenyl)-piperazine



To a stirred solution of 1-(2-ethylphenyl)piperazine (0.19 g; 1.0 mmol), 4-(5-benzimidazolylcarbonylamino)phenylacetic acid (0.329 g; 1.10 mmol), HOBt (0.14 g; 1.0 mmol), and EDC (0.230 g; 1.20 mmol) in DMF (30 mL) was added DIEA (0.23 mL; 1.3 mmol). The reaction was stirred at ambient temperature for 18 h and the

- 79 -

solvent was evaporated under reduced pressure. The residue was partitioned between CH₂Cl₂ and saturated aqueous NaHCO₃. The organic phase was separated and washed with saturated aqueous NaHCO₃ and brine. The organic phase was dried (MgSO₄), filtered, and the solvent was evaporated under reduced pressure. The residue was purified by pressurized silica gel column chromatography using 93:7:0.35 CH₂Cl₂:MeOH:NH₄OH as eluant. Evaporation of the product-containing fractions under reduced pressure gave the title compound as an amorphous solid.

¹H-NMR: Consistent with structure

TLC: silica gel, 90:10:0.5 CH₂Cl₂:MeOH:NH₄OH:

single component, R_f = 0.38

FABMS: M+H @ m/e = 468

HPLC: 99%, retention time 7.33 min

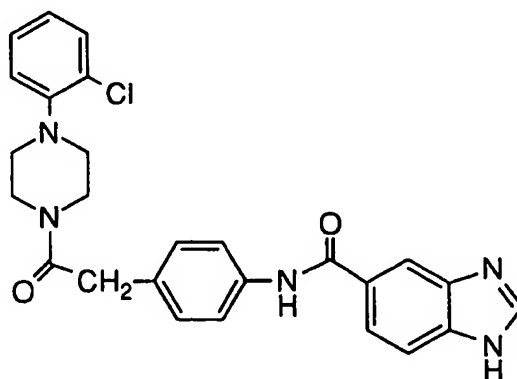
Anal. cal'd for C₂₈H₂₉N₅O₂•0.3 CH₂Cl₂:

C, 68.94; H, 6.05; N, 14.20

Found: C, 69.08; H, 7.73; N, 14.19

EXAMPLE 29

1-(4-(5-Benzimidazolylcarbonylamino)phenylacetyl)-4-(2-chlorophenyl)piperazine



- 80 -

To a stirred solution of 1-(2-chlorophenyl)piperazine (0.20 g; 1.0 mmol), 4-(5-benzimidazolylcarbonylamino)phenylacetic acid (0.329 g; 1.10 mmol), HOBt (0.14 g; 1.0 mmol), and EDC (0.230 g; 1.20 mmol) in DMF (30 mL) was added DIEA (0.23 mL; 1.3 mmol).

The reaction was stirred at ambient temperature for 18 h and the solvent was evaporated under reduced pressure. The residue was partitioned between CH₂Cl₂ and saturated aqueous NaHCO₃. The organic phase was separated and washed with saturated aqueous NaHCO₃ and brine. The organic phase was dried (MgSO₄), filtered, and the solvent was evaporated under reduced pressure. The residue was purified by preparative reverse phase HPLC using an H₂O:CH₃CN gradient containing 0.1% TFA. Lyophilization of the product-containing fractions gave the TFA salt of the title compound as an amorphous solid.

¹H-NMR: Consistent with structure

TLC: silica gel, 90:10:0.5 CH₂Cl₂:MeOH:NH₄OH:
single component, R_f = 0.32

FABMS: M+H @ m/e = 473, 475

HPLC: 99%, retention time 7.17 min

Anal. cal'd for C₂₆H₂₄ClN₅O₂•1.4 TFA•0.15 H₂O:

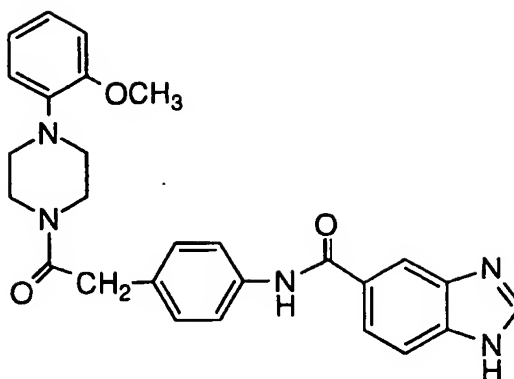
C, 54.36; H, 4.07; N, 11.01

Found: C, 54.33; H, 4.05; N, 11.11

EXAMPLE 30

1-(4-(5-Benzimidazolylcarbonylamino)phenylacetyl)-4-(2-methoxyphenyl)piperazine

- 81 -



To a stirred solution of 1-(2-methoxyphenyl)piperazine (0.19 g; 1.0 mmol), 4-(5-benzimidazolylcarbonylamino)phenylacetic acid (0.329 g; 1.10 mmol), HOBT (0.14 g; 1.0 mmol), and EDC (0.230 g; 1.20 mmol) in DMF (30 mL) was added DIEA (0.23 mL; 1.3 mmol).

The reaction was stirred at ambient temperature for 18 h and the solvent was evaporated under reduced pressure. The residue was partitioned between CH_2Cl_2 and saturated aqueous NaHCO_3 . The organic phase was separated and washed with saturated aqueous NaHCO_3 and brine. The organic phase was dried (MgSO_4), filtered, and the solvent was evaporated under reduced pressure. The residue was purified by preparative reverse phase HPLC using an $\text{H}_2\text{O}:\text{CH}_3\text{CN}$ gradient containing 0.1% TFA. Lyophilization of the product-containing fractions gave the TFA salt of the title compound as an amorphous solid.

^1H -NMR: Consistent with structure

TLC: silica gel, 90:10:0.5 CH_2Cl_2 :MeOH: NH_4OH : single component, $R_f = 0.33$

FABMS: $\text{M}+\text{H}^+$ @ $m/e = 470$

HPLC: 99%, retention time 4.73 min

Anal. cal'd for $\text{C}_{27}\text{H}_{27}\text{N}_5\text{O}_3 \cdot 2.05 \text{ TFA} \cdot 0.4 \text{ H}_2\text{O}$:

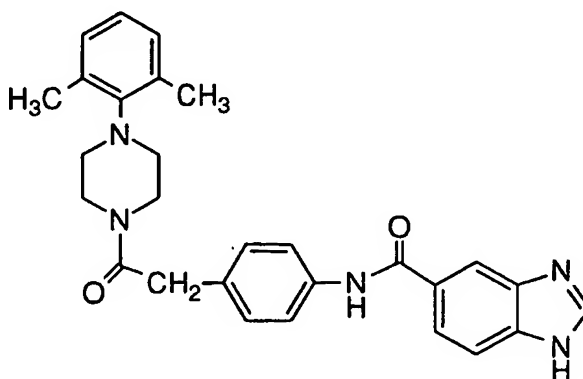
C, 52.57; H, 4.23; N, 9.86

Found: C, 52.57; H, 4.19; N, 9.88

- 82 -

EXAMPLE 31

1-(4-(5-Benzimidazolylcarbonylamino)phenylacetyl)-4-(2,6-dimethylphenyl)piperazine



To a stirred solution of 1-(2,6-dimethylphenyl)piperazine (0.19 g; 1.0 mmol), 4-(5-benzimidazolylcarbonylamino)phenylacetic acid (0.329 g; 1.10 mmol), HOBT (0.14 g; 1.0 mmol), and EDC (0.230 g; 1.20 mmol) in DMF (30 mL) was added DIEA (0.23 mL; 1.3 mmol). The reaction was stirred at ambient temperature for 18 h and the solvent was evaporated under reduced pressure. The residue was partitioned between CH₂Cl₂ and saturated aqueous NaHCO₃. The organic phase was separated and washed with saturated aqueous NaHCO₃ and brine. The organic phase was dried (MgSO₄), filtered, and the solvent was evaporated under reduced pressure. The residue was purified by pressurized silica gel column chromatography using 93:7:0.35 CH₂Cl₂:MeOH:NH₄OH as eluant. Evaporation of the product-containing fractions under reduced pressure gave the title compound as an amorphous solid.

¹H-NMR: Consistent with structure

TLC: silica gel, 90:10:0.5 CH₂Cl₂:MeOH:NH₄OH:
single component, R_f = 0.38

FABMS: M+H @ m/e = 468

HPLC: 99%, retention time 7.75 min

- 83 -

Anal. cal'd for $C_{28}H_{29}N_5O_2 \cdot 0.76 H_2O$:

C, 69.88; H, 6.39; N, 14.55

Found: C, 69.87; H, 6.08; N, 14.39

5

EXAMPLE 32

As a specific embodiment of an oral composition of a compound of this invention, 100 mg of the compound of Example 5 is formulated with sufficient finely divided lactose to provide a total amount of 580 to 590 mg to fill a size O hard gel capsule.

10

EXAMPLE 33

RADIOLIGAND BINDING ASSAYS

15

The high affinity binding of [3H]oxytocin (OT) to uterine tissue and [3H]arginine vasopressin (AVP) to liver (AVP-V₁ site) and kidney (AVP-V₂ site) tissue was determined using crude membrane preparations as described previously [Pettibone, D.J., et al., *J. Pharmacol. and Exper. Ther.*, 256(1): 304-308 (1991)]. Uterine tissue was taken from nonpregnant adult Sprague-Dawley rats (Taconic Farms, Germantown, NY) pretreated (18-24 h) with diethylstilbestrol propionate (DES; 300 μ g/kg, i.p.). Uterine tissue (full thickness) was also taken with informed consent from nonlabor pregnant women undergoing cesarean section at 38 to 39 weeks gestation (Oregon Health Sciences Center, Portland, OR). Liver and kidney medulla samples were taken from male rats and from human surgical and early postmortem donors (National Disease Research Interchange, Philadelphia PA; Analytical Biological Services, Wilmington, DE).

20

25

Competition studies were conducted at equilibrium using 1 nM [3H]OT or 0.5 nM [3H]AVP in the following buffer: 50 mM Tris, 5 mM $MgCl_2$, 0.1% bovine serum albumin. Nonspecific binding was determined using 1 μ M unlabeled OT or AVP in their respective assays. The binding reactions were initiated by the addition of tissue preparation and terminated by filtration using a Skatron cell harvester

30

- 84 -

(model 7019, Skatron, Inc., Sterling, VA). K_i values were calculated for each compound using three to six separate IC_{50} determinations ($K_i = IC_{50}/[1 - c/K_d]$); [Cheng, Y-C; Prusoff, W.H.; *Biochem Pharmacol* 22:3099 (1973)] with mean K_d values obtained from replicate ($n = 3$) equilibrium saturation binding assays (10 point, 100 fold concentration range): [3H]OT rat uterus, 0.69 nM; human myometrium, 1.1 nM; [3H]AVP: rat liver, 0.21 nM; rat kidney, 0.27 nM; human liver, 0.27 nM; human kidney, 1.4 nM. Computer analysis of the saturation assays by EBDA/LIGAND [McPherson, G.A.: *Kinetic, Ebda, Ligand, Lowry: A Collection of Radioligand Binding Analysis Programs*, Elsevier Science Publishers, Amsterdam (1985)] indicated that both radioligands apparently bound to single sites in all tissues examined. The final protein concentration for the various tissues in each assay ranged from 150 to 300 $\mu g/ml$ [Lowry, P.H.; Rosebrough, N.J.; Farr, A.L.; Randall, R.J.; *J. Biol. Chem.*, 193:265-275 (1951)].

IC_{50} values were determined for the [3H]OT and [3H]AVP binding assays by linear regression of the relation log concentration of compound vs. percent inhibition of specific binding. Data is either reported as a given percentage of inhibition at a specified concentration, or if an IC_{50} was calculated, as a nanomolar concentration. Representative IC_{50} values of the compounds of the instant invention for rat [3H]OT are given below.

	Example	Result For [3H]OT (nM)
25	1	400
	2	120
	4	1600
	6	540
	7	80
	8	30
30	9	34
	11	21
	12	20
	14	24
	15	28

- 85 -

EXAMPLE 34

EXEMPLARY FUNCTIONAL ASSAYS

5

1. Antagonism of OT-stimulated contractions of the rat isolated uterus

As described previously [Pettibone et al., 1989], uterine horns removed from adult Sprague-Dawley rats (Taconic Farms, Germantown, NY) treated 18 h earlier with DES (0.25 mg/kg, i.p.) were mounted longitudinally in standard tissue baths (30°C) containing a physiological buffer solution and oxygenated continuously. Tissues were connected to isometric force displacement transducers and placed under a tension of 1 g. Contraction of the longitudinal muscle layer was amplified and recorded on a polygraph. A cumulative concentration-response curve was obtained using a 4 min exposure at each concentration of OT. Once the maximal effect (E_{max}) was attained, the tissues were washed repeatedly for 75 min. at which time antagonist or vehicle was added to the tissue bath, and 45 min later, a second concentration-response curve to OT was constructed. The concentration of OT producing 50% of E_{max} before and after treatment was determined by regression analysis. Dose ratios (EC_{50} after treatment/ EC_{50} before) were corrected, if indicated, by a factor derived from concurrent vehicle-treated tissues. The results were analyzed for competitiveness, and the pA_2 value was estimated from standard Schild plot [Arunlakshana and Schild, 1959].

15
20
252. OT antagonist activity in the nonpregnant rat

The procedure for measuring isometric contraction of the uterus *in situ* was adapted from that of Chan et al. [1974] as previously described [Pettibone et al., 1989]. Sprague-Dawley rats (200-300 g, Taconic Farms, Germantown, NY) pretreated with DES (0.25 mg/kg, i.p.; 18 h) were anesthetized with urethane (1.75 g/kg, i.p.), a tracheal cannula was inserted, and a femoral vein was cannulated. The left uterine horn was exposed, and the anterior part of the horn was secured with surgical silk to an anchor post. A second ligature about 3 cm

30

- 86 -

posterior to the first tie was connected to a force transducer and maintained at a tension of 1 g. Signals from the transducer were amplified and recorded. The contractile response of the uterus to OT was quantified by computerized measurement of the area under the contraction-time curve for a 10-min period immediately after the injection of OT. The following protocol was adopted for most experiments. OT (1 µg/kg; approximately an ED50 dose) was injected i.v. every 35 min for a total of eight times. The contractile response obtained from the third injection was set as 100%. Areas determined after each injection was expressed as a percentage of the area obtained for the third injection. Fifteen min before the fourth injection of OT, vehicle or test compound was infused i.v. for 10 min. The dose of test compound required to reduce the response to OT by 50% (AD50) was calculated from the contractile areas obtained after the fourth injection of OT (i.e., 5 min postinfusion of test compound). Percent antagonism (relative to the concurrent vehicle-treated group) was determined for each dose of test compound and AD50 was estimated by regression analysis.

20

REFERENCES

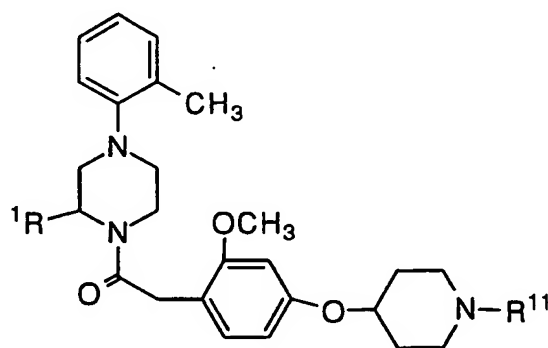
- Arunklaskshana O. Schild HO (1959); Some quantitative uses of drug antagonists. Br J pharmacol 14:48-58.
- 25 Pettibone DJ, Clineschmidt BV, Anderson PS, Freidinger RM, Lundell GF, Koupal LR, Schwartz CD, Williamson JM, Goetz MA, Hensens OD, Liesch JM, Springer JP (1989): A structurally unique, potent and selective oxytocin antagonist derived from *Streptomyces silvensis*. Endocrinology 125:217-222.
- 30 Chan WY, Nestor JJ, Ferger MF, DuBigneaud V (1974): Inhibition of oxytocic responses to oxytocin in pregnant rats by [l-L-penicillamine]-oxytocin. Proc Soc Exp Biol Med 146:364-366.

- 87 -

In addition to those compounds specifically exemplified above, additional compounds of the present invention are set forth in tabular form below. These compounds are synthesized by use of the synthetic routes and methods described in the above Schemes and Examples and variations thereof well known to those of ordinary skill in the art, and not requiring undue experimentation. All variables listed in the Tables below are with reference to the following generic structure:

10

15

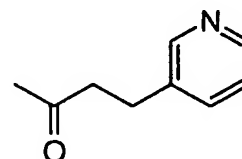
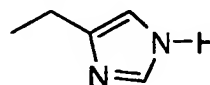


20

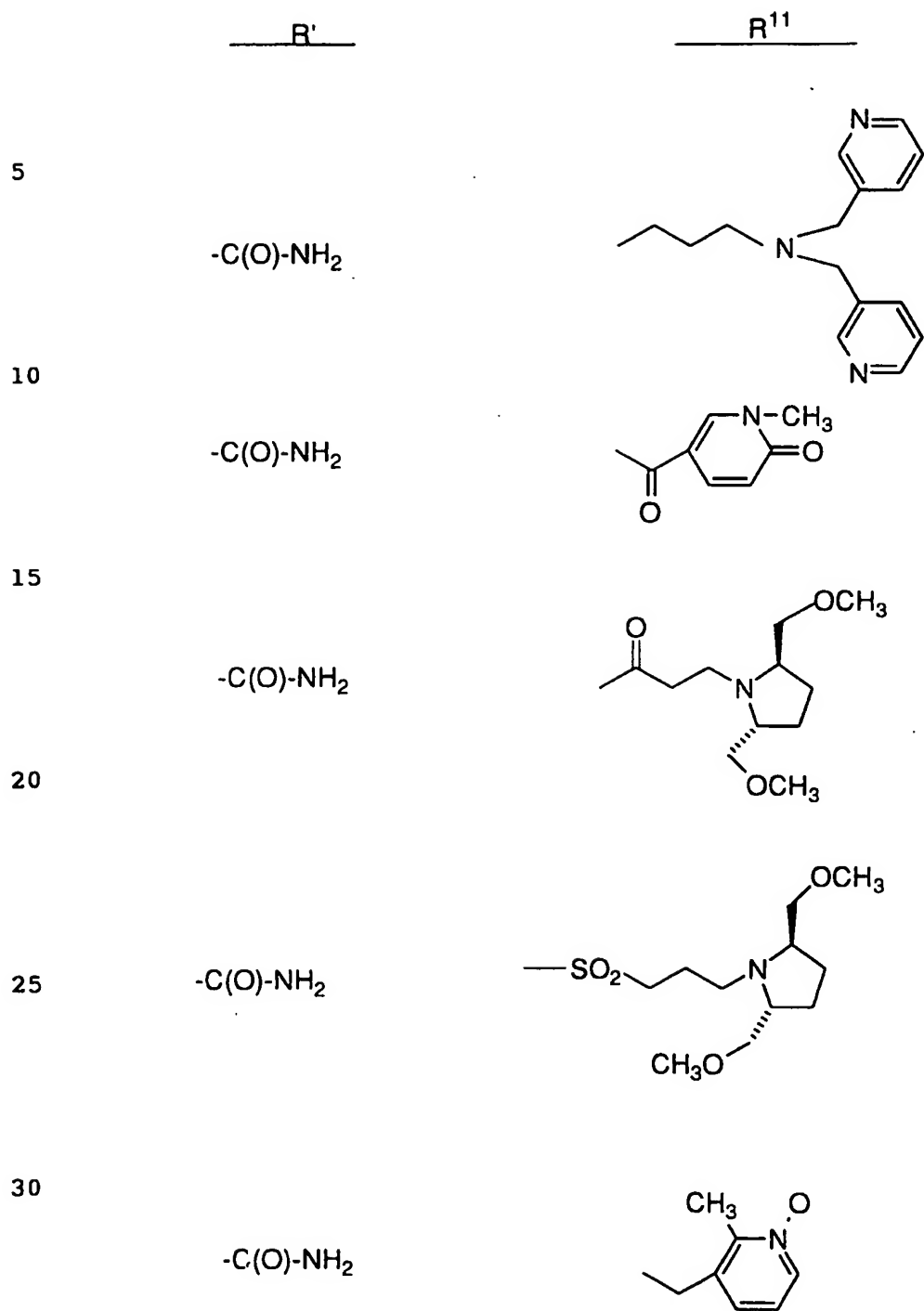
TABLE

25


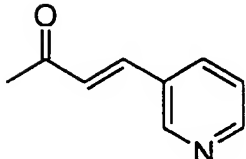
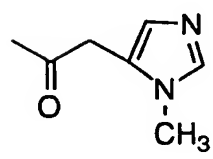
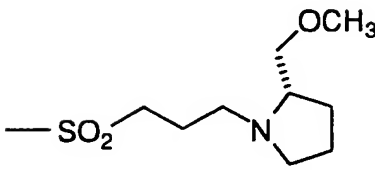
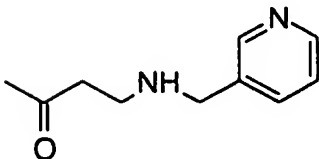
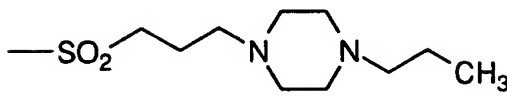
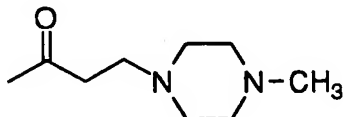
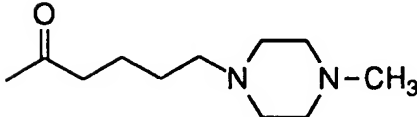
30

R'R¹¹-C(O)-NH₂-CH₂-CH(CH₃)₃-C(O)-NH₂-C(O)-NH₂

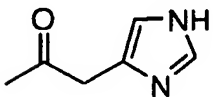
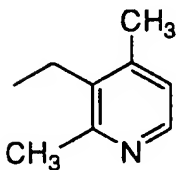
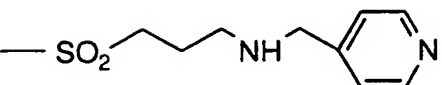
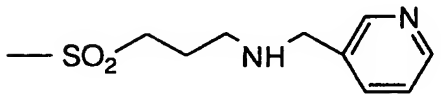
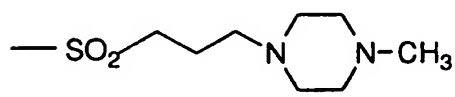
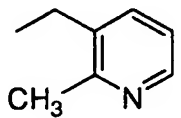
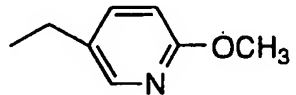
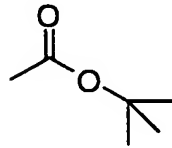
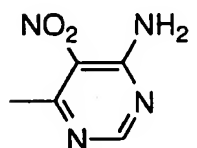
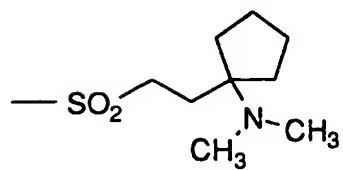
- 88 -



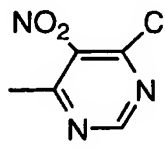
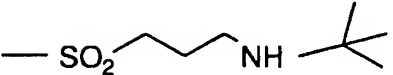
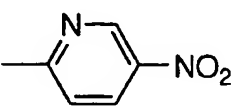
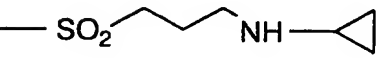
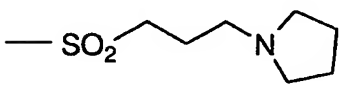
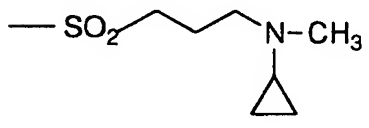
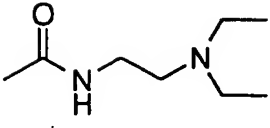
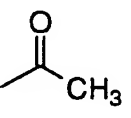
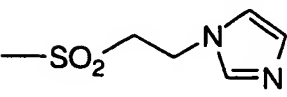
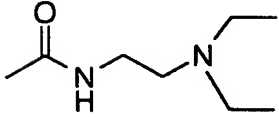
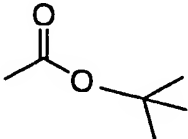
- 89 -

	$\frac{R'}{-C(O)-NH_2}$	$\frac{R^{11}}{\text{CH}_2\text{CH}_2\text{CN}}$
5	$-C(O)-NH_2$	
10	$-C(O)-NH_2$	 H
15	$-C(O)-NH_2$	
20	$-C(O)-NH_2$	
25	$-C(O)-NH_2$	
30	$-C(O)-NH_2$	
	$-C(O)-NH_2$	
	$-C(O)-NH_2$	

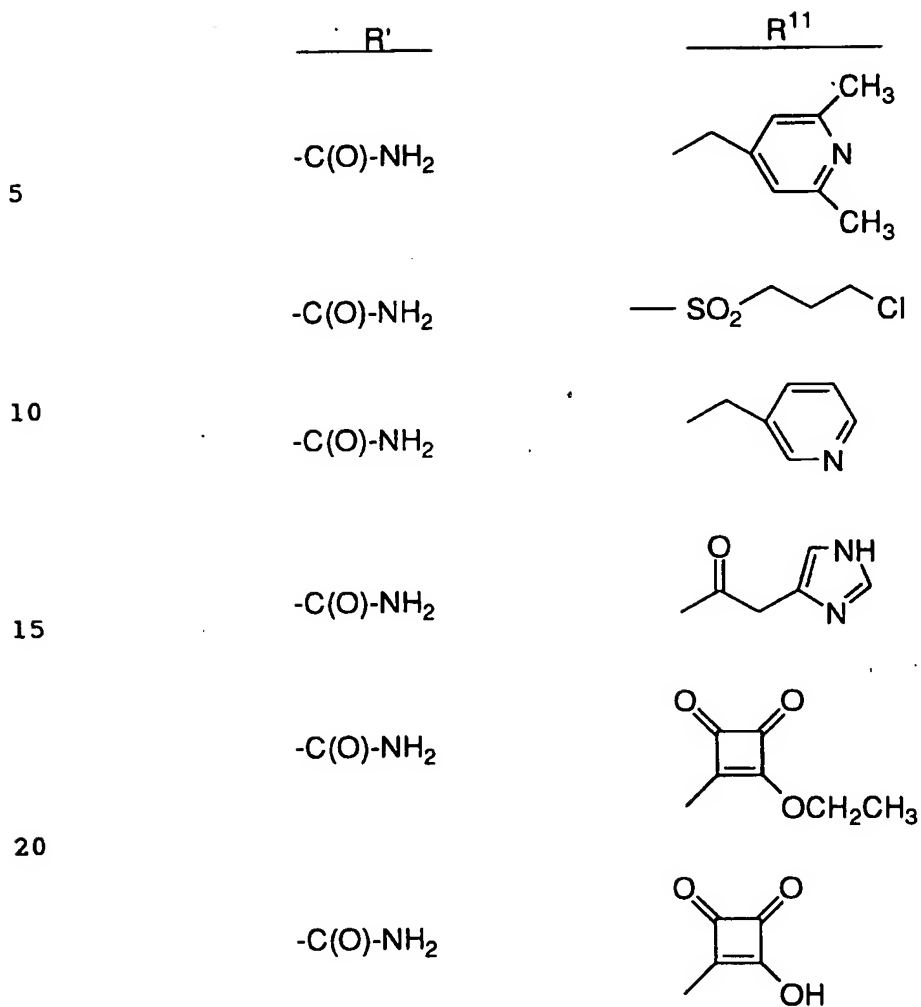
- 90 -

	R'	R^{11}
5	$-\text{C}(\text{O})-\text{NH}_2$	
	$-\text{C}(\text{O})-\text{NH}_2$	
10	$-\text{C}(\text{O})-\text{NH}_2$	
	$-\text{C}(\text{O})-\text{NH}_2$	
15	$-\text{C}(\text{O})-\text{NH}_2$	
20	$-\text{C}(\text{O})-\text{NH}_2$	
	$-\text{C}(\text{O})-\text{NH}_2$	
25	$-\text{C}(\text{O})-\text{NH}_2$	
30	$-\text{C}(\text{O})-\text{NH}_2$	
	$-\text{C}(\text{O})-\text{NH}_2$	

- 91 -

	<u>R'</u>	<u>R¹¹</u>
5	-C(O)-NH ₂	
	-C(O)-NH ₂	
10	-C(O)-NH ₂	
	-C(O)-NH ₂	
15	-C(O)-NH ₂	
20	-C(O)-NH ₂	
25		
	-C(O)-NH ₂	
30		

- 92 -

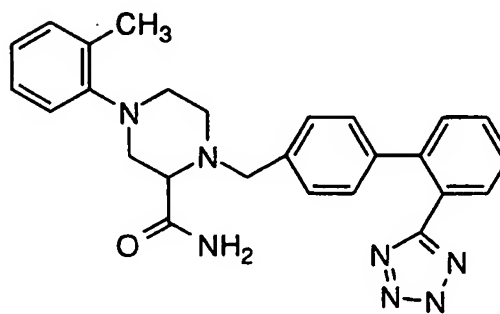
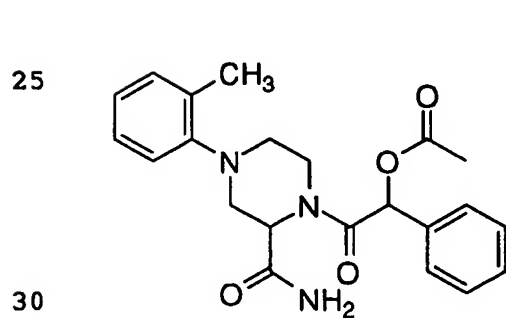
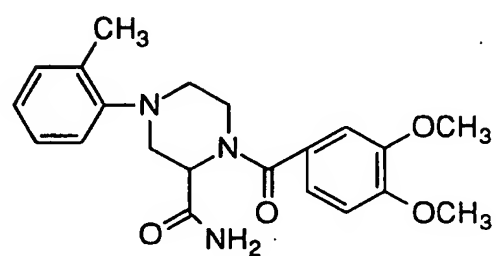
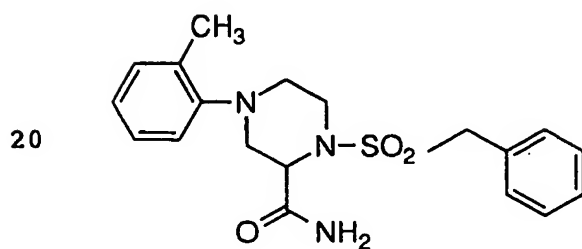
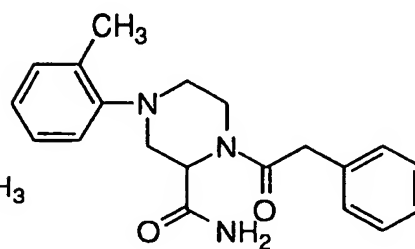
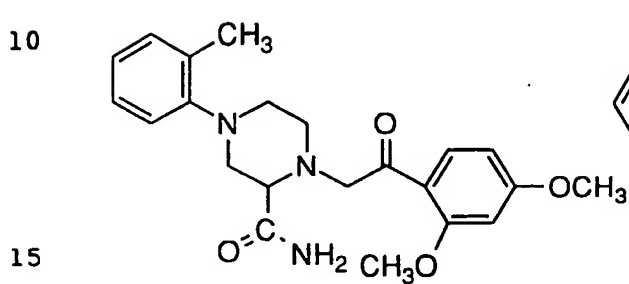
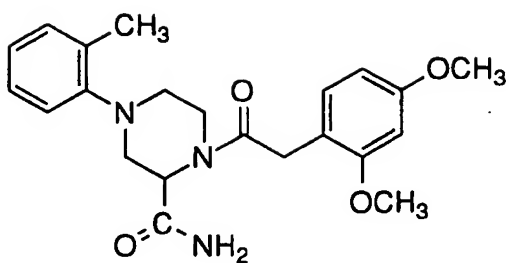
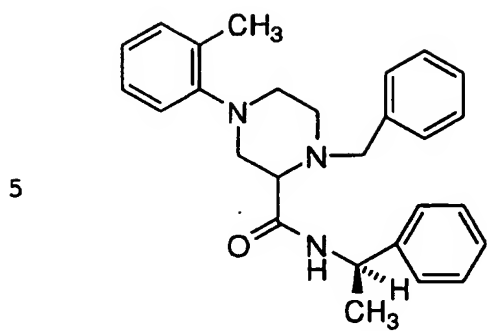


25

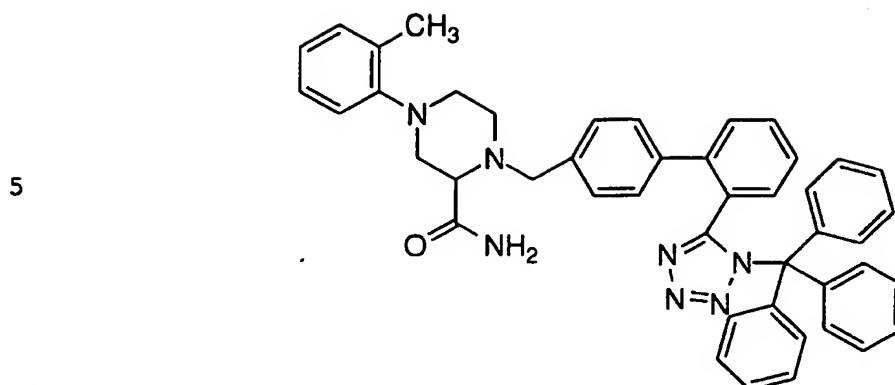
Also included within the present invention are the following compounds which can be synthesized by use of synthetic routes and methods described in the above schemes and Examples and variations thereof well known to those of ordinary skill in the art.

30

- 93 -



- 94 -



While the invention has been described and illustrated with reference to certain preferred embodiments thereof, those skilled in the art will appreciate that various changes, modifications and substitutions can be made therein without departing from the spirit and scope of the invention. For example, effective dosages other than the preferred dosages as set forth hereinabove may be applicable as a consequence of variations in the responsiveness of the mammal being treated for prevention of preterm labor, or for other indications for the compounds of the invention indicated above. Likewise, the specific pharmacological responses observed may vary according to and depending upon the particular active compound selected or whether there are present pharmaceutical carriers, as well as the type of formulation and mode of administration employed, and such expected variations or differences in the results are contemplated in accordance with the objects and practices of the present invention. It is intended, therefore, that the invention be limited only by the scope of the claims which follow and that such claims be interpreted as broadly as is reasonable.

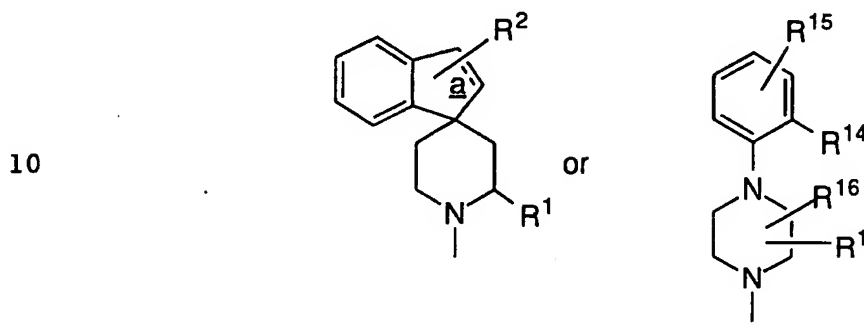
30

- 95 -

WHAT IS CLAIMED IS:

1. A compound of the formula X-Y-R, wherein

5 X is



15 a is a single or double bond;

Y is selected from the group consisting of -COO-, -CONR²-,
-C(=NR²)-, -SO₂-, -CO-(CH₂)_n-, -(CH₂)_p- and -(CH₂)_p-CO-;

20 R is selected from the group consisting of furyl, thienyl, pyrrolyl, naphthyl, indolyl, benzimidazolyl, tetrahydronaphthyl, pyridyl, quinolyl, unsubstituted or substituted cyclohexyl where said substituent is R⁴, and unsubstituted or substituted phenyl where said substituents are one or more of R⁵, R⁶ or R⁷;

25 R¹ is selected from the group consisting of hydrogen, C₁-5 alkyl, cyano, carboxyl, phenyl, -CONHR², -CONR²R², -CO₂R³, -COR³, -(CH₂)_m-OR², -(CH₂)_p-S(O)_r-R², -(CH₂)_m-CO₂R², -(CH₂)_m-N₃, -(CH₂)_m-NH₂ and -(CH₂)_m-NR²R²;

30 R² is selected from the group consisting of hydrogen, benzyl, C₃-8 cycloalkyl and C₁-5 alkyl;

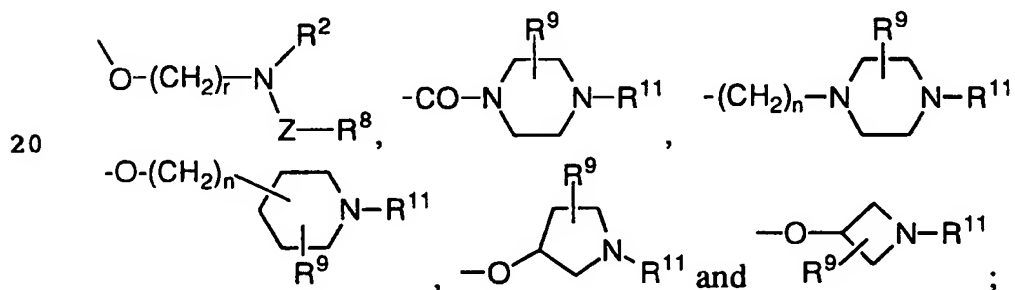
R³ is selected from the group consisting of C₁-5 alkyl and phenyl;

- 96 -

R⁴ is selected from the group consisting of hydrogen, oxo, hydroxyl, C₁-5 alkyl and C₁-5 alkoxy;

5 R⁵ and R⁶ are each independently selected from the group consisting of hydrogen, C₁-5 alkyl, C₁-5 alkoxy, trifluoromethoxy, 2,2,2-trifluoroethoxy, allyloxy, propargyloxy, trifluoromethyl, C₃-8 cycloalkyloxy, cyclopropylmethoxy, hydroxy, hydroxyalkyl, cyano, nitro, amino, halogen, $-(CH_2)_n-CO-R^{10}$, $-O(CH_2)_n-CO-R^{10}$, $-(CH_2)_n-R^{10}$, $-OCH_2(CH_2)_q-R^{10}$, $-OCH_2(CH_2)_q-N(R^2)-R^{17}$ and
10 $-(CH_2)_n-N(R^2)-R^{17}$;

R⁷ is selected from the group consisting of hydrogen, C₁-5 alkyl, halogenated C₁-5 alkyl, phenyl, phenyl-C₁-5 alkyl, amino C₂-5 alkoxy, C₁-5 alkoxy, carboxyl, carboxy-
15 C₁-5 alkyl, C₁-5 alkoxy carbonyl, halogen, hydroxyl,



25 R⁸ is selected from the group consisting of hydrogen, Het, C₁-5 alkoxy, unsubstituted C₁-5 alkyl and substituted C₁-5 alkyl where said substituent is selected from the group consisting of carboxyl, hydroxyl, amino, $-N(R^2)_2$, $-NHR^2$, C₁-10 alkoxy carbonylamino and Het;

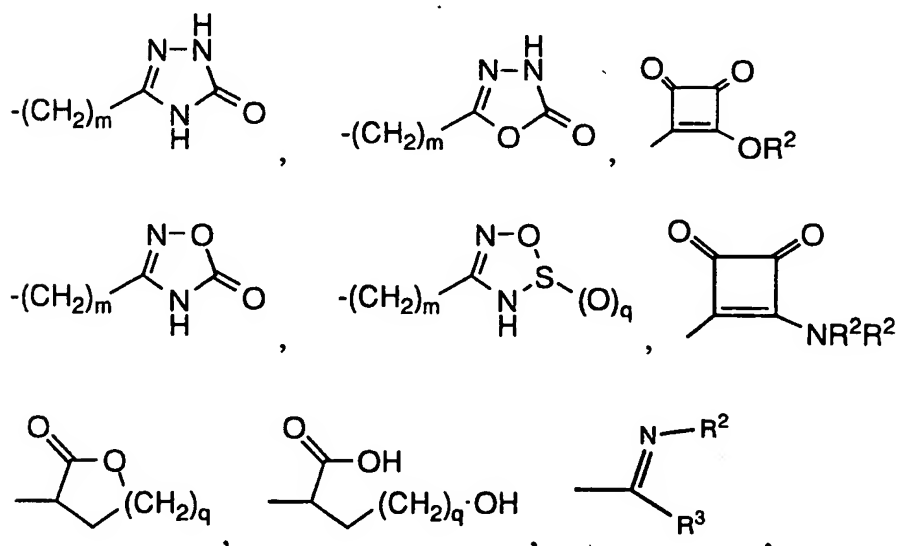
30 R⁹ is selected from the group consisting of hydrogen, C₁-5 alkyl, hydroxyalkyl, methylthioalkyl, methylsulfonylalkyl, methylsulfonyl, cyano, carbamoyl, $-(CH_2)_n-CO_2H$, $-(CH_2)_p-R^{10}$ and $-(CH_2)_p-COR^{10}$;

- 97 -

R¹⁰ is selected from the group consisting of hydroxyl, C₁₋₅ alkoxyl, amino, -N(R²)₂, -NHR², 1-piperazinyl, 4-methyl-1-piperazinyl, pyridinyl, 4-morpholinyl, 1-pyrrolidinyl and 1-piperidinyl;

5 R¹¹ is selected from the group consisting of hydrogen, C₁₋₅ alkoxy carbonyl, C₁₋₅ alkyl carbonyl, C₁₋₅ alkyl, allyl, 5-tetrazolyl, 2-pyrimidinyl, 2-pyrazinyl, 2-pyridyl, 4-pyridyl, 4-piperidinyl, 1-methyl-4-piperidinyl, 4-tetrahydropyranyl, -CO-NH-COR¹², -CO-NH-SO₂R¹², -SO₂-NH-COR¹², -Z-R¹³,

10



25 and substituted C₁₋₁₀ alkyl wherein said substituent on said alkyl is selected from the group consisting of hydroxyl, C₁₋₁₀ alkoxyl, C₁₋₁₀ alkoxy carbonyl, carboxyl, -SO₂NH₂, amino, -N(R²)₂, -NHR², 1-piperazinyl, 4-methyl-1-piperazinyl, pyridinyl, quinolinyl, 4-morpholinyl, 1-pyrrolidinyl, imidazolyl, 4-piperidinyl, 1-methyl-4-piperidinyl, 1-piperidinyl, 5-tetrazolyl, unsubstituted, mono-, di- or tri-substituted pyridyl wherein said substituents on said pyridyl are

30 independently selected from halogen, C₁₋₅ alkoxyl, alkylendioxy, C₁₋₅ alkyl, C₁₋₁₀ alkoxy carbonyl, carboxyl, trifluoromethyl, -SO₂CH₃ or -SO₂NH₂, and unsubstituted, mono-, di- or tri-substituted phenyl

- 98 -

wherein said substituents on said phenyl are independently selected from the group consisting of halogen, C₁-5 alkoxyl, alkylenedioxy, C₁-5-alkyl, C₁-10 alkoxycarbonyl, carboxyl, trifluoro-methyl, -SO₂CH₃ and -SO₂NH₂;

5

R¹² is selected from the group consisting of C₁-10 alkyl, trifluoromethyl, and phenyl optionally substituted with one to three members of the group consisting of C₁-5 alkyl, C₁-10 alkoxyl, halogen and trifluoromethyl;

10

R¹³ is selected from the group consisting of C₁-10 alkyl, C₁-10 alkoxyl, amino, carboxyl, phenyl, vinyl, morpholinyl, piperidinyl, pyrrolidinyl, pyridinyl, piperazinyl, 1-methyl-4-piperazinyl, 1-alkoxycarbonyl-4-piperidinyl, -N(R²)-(CH₂)_i-R¹⁰, substituted phenyl wherein the substituent is selected from the group consisting of nitro, C₁-10 alkoxyl, amino, monoalkylamino, dialkylamino, halogen, 1-piperazinyl, 4-piperidinyloxy, 4-methyl-1-piperazinyl, C₁-10 alkoxycarbonyl, carboxyl, amino C₁-10 alkyl, monoalkylaminoalkyl, dialkylaminoalkyl, 4-morpholinylalkyl, 1-piperazinylalkyl, and 4-methyl-1-piperazinylalkyl; and substituted C₁-10 alkyl wherein the substituent is selected from the group consisting of phenyl, hydroxyl, C₁-10 alkoxyl, C₁-10 alkoxycarbonyl, carboxyl, halogen, amino, -N(R²)₂, -NHR², 1-piperazinyl, 1-methyl-4-piperazinyl, pyridinyl, 4-morpholinyl, pyrrolidinyl, imidazolyl, 5-tetrazolyl, azetidiny, piperidinyl, and substituted phenyl wherein the substituent is selected from the group consisting of nitro, C₁-10 alkoxyl, amino, monoalkylamino, dialkylamino, halogen, 1-piperazinyl, 4-piperidinyloxy, 4-methyl-1-piperazinyl, C₁-10 alkoxycarbonyl, carboxyl, aminoalkyl, monoalkylaminoalkyl, dialkylaminoalkyl, 4-morpholinylalkyl, 1-piperazinylalkyl, and 4-methyl-1-piperazinylalkyl;

15

20

25

30

R¹⁴ and R¹⁵ are each independently selected from the group consisting of hydrogen, C₁-5 alkyl, C₁-5 alkoxyl, halogen, nitro and cyano;

- 99 -

R¹⁶ is selected from the group consisting of hydrogen and oxo;

5 R¹⁷ is selected from the group consisting of hydrogen, R² and -Z-R¹⁸;

R¹⁸ is selected from the group consisting of C₁₋₅ alkoxyl, Het,
unsubstituted or substituted C₁₋₅ alkyl wherein said substituent is Het
and unsubstituted or substituted C₂₋₅ alkenyl wherein said substituent is
10 Het;

Het is selected from the group consisting of imidazolyl, piperidinyl,
C₁₋₅ alkyl-substituted piperidinyl, piperazinyl, C₁₋₅ alkyl-substituted
piperazinyl, benzimidazolyl, carboxymethyl-substituted benzimidazolyl,
indolyl, morpholiny, tetrazolyl, C₁₋₅ alkylcarbonyl-substituted
15 piperidinyl, C₁₋₅ alkoxy carbonyl-substituted piperidinyl, pyrrolidinyl,
C₁₋₅ alkyl-substituted pyrrolidinyl, and pyridinyl;

Z is -CO- or -SO₂-;

20 i is an integer of from 2 to 5;

m is an integer of from 1 to 5;

25 n is an integer of from 0 to 3;

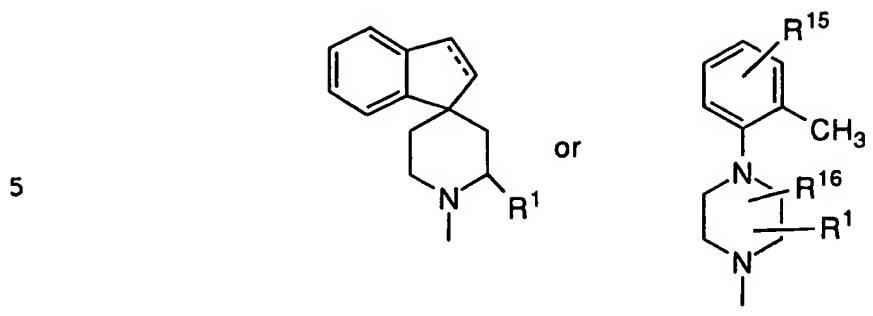
p is an integer of from 1 to 3; and

q is an integer of from 1 to 2;

30 r is an integer of from 0 to 2;

provided that when X is

- 100 -



10 and Y is -SO₂-, -CO-(CH₂)_n- or -(CH₂)_p-; and
 R¹⁵ is hydrogen, methyl or halogen; and
 R is thienyl, naphthyl, indolyl, pyridyl, quinolyl, unsubstituted or
 substituted cyclohexyl where said substituent is R⁴, or unsubstituted or
 substituted phenyl where said substituents are one or more of R⁵, R⁶ or
 15 R⁷; then R¹ is not hydrogen;

and the pharmaceutically acceptable salts and esters thereof.

2. The compound of Claim 1, wherein

20 Y is selected from the group consisting of -SO₂-, -CO-(CH₂)_n- and
 -(CH₂)_p-;

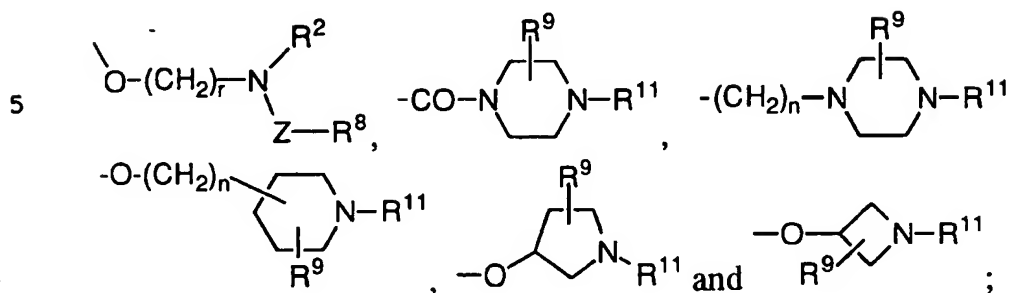
R is unsubstituted or substituted phenyl where said substituents are one
 or more of R⁵, R⁶ or R⁷;

25 R¹ is selected from the group consisting of hydrogen, cyano, phenyl,
 -CONHR², -CONR²R², -(CH₂)_m-OR², -(CH₂)_p-S(O)_r-R²,
 -(CH₂)_m-CO₂R², -(CH₂)_m-N₃, -(CH₂)_m-NH₂ and -(CH₂)_m-NR²R²;

30 R⁵ and R⁶ are each independently selected from the group consisting of
 hydrogen, C₁₋₅ alkyl, C₁₋₅ alkoxy, halogen, -(CH₂)_n-CO-R¹⁰,
 -O(CH₂)_n-CO-R¹⁰, -(CH₂)_n-R¹⁰, -OCH₂(CH₂)_q-R¹⁰,
 -OCH₂(CH₂)_q-N(R²)-R¹⁷ and -(CH₂)_n-N(R²)-R¹⁷;

- 101 -

R^7 is selected from the group consisting of hydrogen,



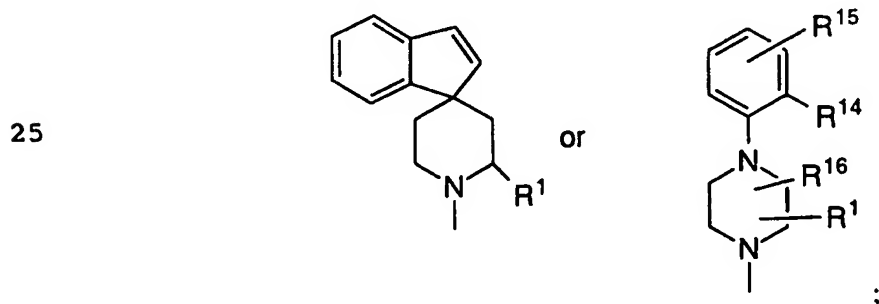
R^9 is hydrogen;

R^{14} is selected from the group consisting of C₁-5 alkyl, C₁-5 alkoxy and halogen; and

R^{15} is selected from the group consisting of hydrogen and C₁-5 alkyl; and the pharmaceutically acceptable salts and esters thereof.

3. The compound of Claim 2, wherein

X is



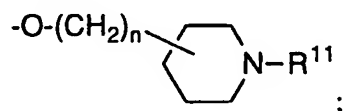
Y is selected from the group consisting of $-(CH_2)_p-$ and $-CO-(CH_2)_n-$;

R^2 is selected from the group consisting of hydrogen, C₃-8 cycloalkyl and C₁-5 alkyl;

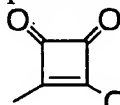
- 102 -

R⁵ and R⁶ are each independently selected from the group consisting of hydrogen, C₁-5 alkoxy, halogen and -(CH₂)_n-N(R²)-R¹⁷;

5 R⁷ is selected from the group consisting of hydrogen and



10 R¹¹ is selected from the group consisting of hydrogen,



C₁-5 alkylcarbonyl, -Z-R¹³, and substituted C₁-5 alkyl wherein said substituent on said alkyl is unsubstituted, mono-, di- or tri-substituted pyridyl wherein said substituents on said pyridyl are
15 independently selected from the group consisting of halogen, C₁-5 alkyl and C₁-5 alkoxy;

R¹³ is selected from the group consisting of unsubstituted C₁-10 alkyl
20 and substituted C₁-10 alkyl wherein said substituent is selected from the group consisting of -N(R²)₂, -NHR² and imidazolyl;

R¹⁷ is -Z-R¹⁸; and

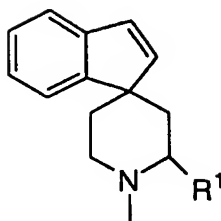
25 Het is selected from the group consisting of imidazolyl, benzimidazolyl, carboxymethyl-substituted benzimidazolyl and indolyl;

and the pharmaceutically acceptable salts and esters thereof.

30 4. The compound of Claim 3, wherein

X is

- 103 -



R¹ is selected from the group consisting of hydrogen, phenyl, cyano and -CONHR²;

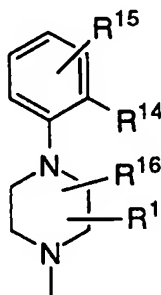
R⁵ is -NH-CO-R¹⁸;

R⁶ and R⁷ are hydrogen; and

R¹⁸ is selected from Het or substituted C₂₋₅ alkenyl wherein said substituent is Het; and the pharmaceutically acceptable salts and esters thereof.

5. The compound of Claim 3, wherein

X is



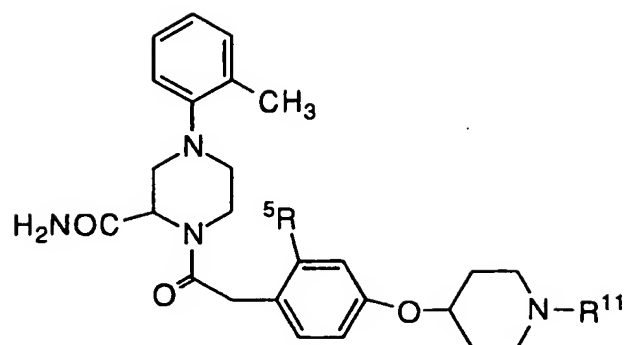
; and

R¹ is selected from the group consisting of hydrogen, -CONHR², -(CH₂)_m-CO₂R², -(CH₂)_m-OR², -(CH₂)_p-S(O)_rR², -(CH₂)_m-N₃, -(CH₂)_m-NH₂ and -(CH₂)_m-NR²R²; and the pharmaceutically acceptable salts and esters thereof.

6. The compound of Claim 5, of the structure

- 104 -

5



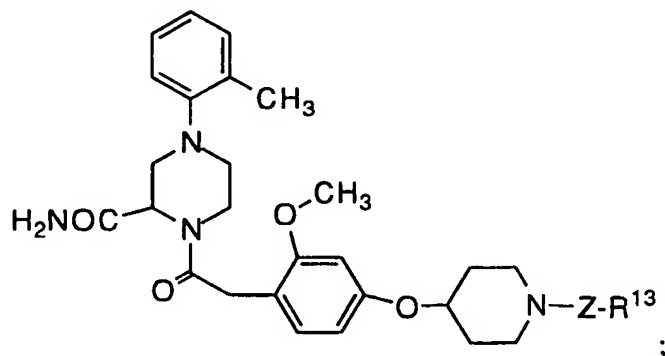
10

wherein R^5 is C_1 -5 alkoxy;
and the pharmaceutically acceptable salts and esters thereof.

7. The compound of Claim 6, of the structure

15

20

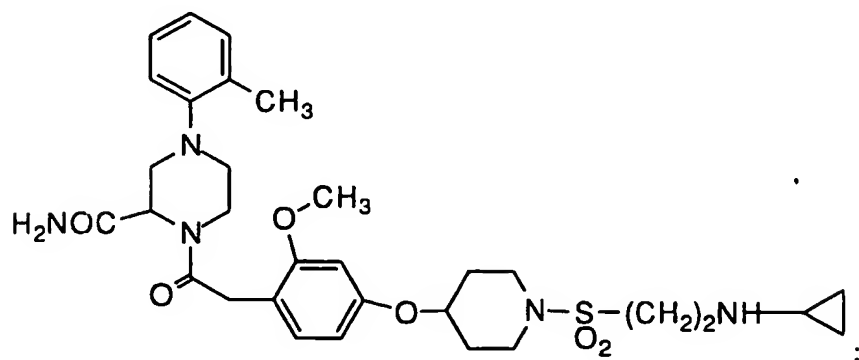


and the pharmaceutically acceptable salts and esters thereof.

25

8. The compound of Claim 7, of the structure

30



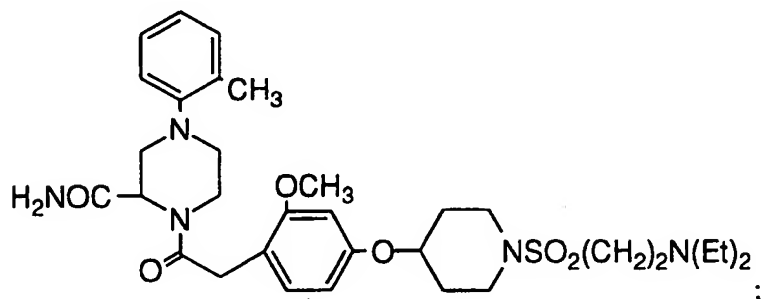
- 105 -

and the pharmaceutically acceptable salts and esters thereof.

9. The compound of Claim 7, of the structure

5

10



and the pharmaceutically acceptable salts and esters thereof.

15

10. A pharmaceutical composition comprising a pharmaceutically acceptable carrier and a pharmacologically effective amount of the compound as claimed in Claim 1.

20

11. A method of eliciting an oxytocin antagonizing effect in a mammal, comprising the step of administering to said mammal a pharmacologically effective amount of the compound as claimed in Claim 1.

25

12. A method of treating preterm labor in a mammal in need thereof, comprising the step of administering to said mammal a pharmacologically effective amount of the compound as claimed in Claim 1.

30

13. A method of stopping labor preparatory to cesarian delivery in a mammal in need thereof, comprising the step of administering to said mammal a pharmacologically effective amount of the compound as claimed in Claim 1.

14. A method of treating dysmenorrhea in a mammal in need thereof, comprising the step of administering to said mammal a

- 106 -

pharmacologically effective amount of the compound as claimed in Claim 1.

5 15. A method of increasing fertility and embryonic survival in a farm animal, comprising administering to the farm animal a pharmacologically effective amount of the compound of Claim 1.

10 16. A method for improving survival of a farm animal neonate comprising controlling timing of parturition to effect delivery of the neonate during daylight hours by administering to a farm animal which is expected to deliver the neonate within 24 hours a pharmacologically effective amount of the compound of Claim 1.

15 17. A method of controlling the timing of estrus in a farm animal, comprising administering to the farm animal a pharmacologically effective amount of the compound of Claim 1.

20 18. A method of antagonizing vasopressin from binding to its receptor site in a mammal, comprising the step of administering to said mammal a pharmacologically effective amount of the compound as claimed in Claim 1.

25 19. A method of inducing vasodilation in a mammal in need thereof, comprising the step of administering to said mammal a pharmacologically effective amount of the compound as claimed in Claim 1.

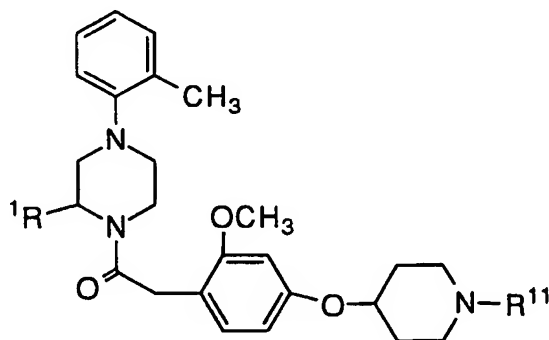
30 20. A method of treating hypertension in a mammal in need thereof, comprising the step of administering to said mammal a pharmacologically effective amount of the compound as claimed in Claim 1.

- 107 -

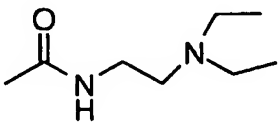
21. A method of inducing diuresis in a mammal in need thereof, comprising the step of administering to said mammal a pharmacologically effective amount of the compound as claimed in Claim 1.

22. A method of inhibiting platelet agglutination in a mammal in need thereof, comprising the step of administering to said mammal a pharmacologically effective amount of the compound as claimed in Claim 1.

23. A compound of the formula

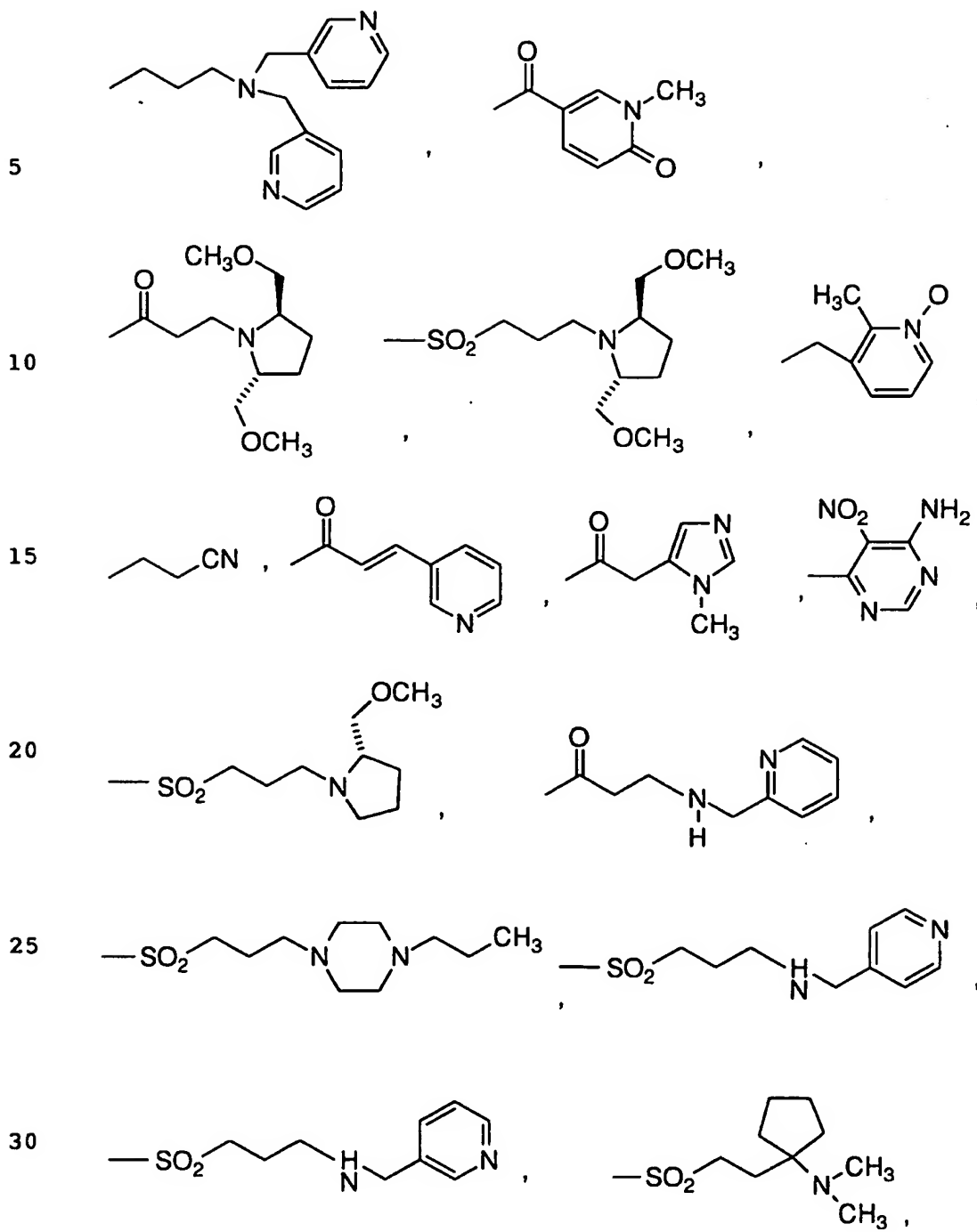


wherein

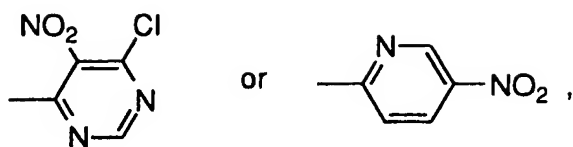
R^1 is selected from $-\text{CONH}_2$ and ; and

R^{11} is selected from C_1 -5 alkylcarbonyl, C_1 -5 alkoxy carbonyl,

- 108 -



- 109 -

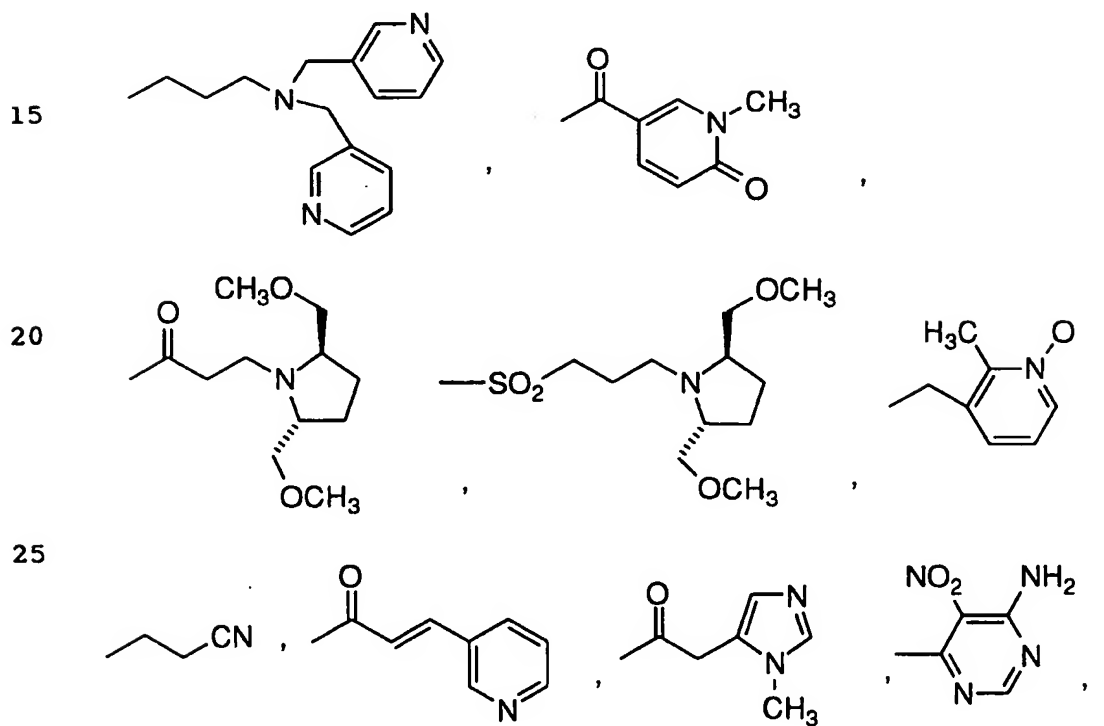


⁵ and the pharmaceutically acceptable salts thereof.

24. The compound of Claim 23, wherein

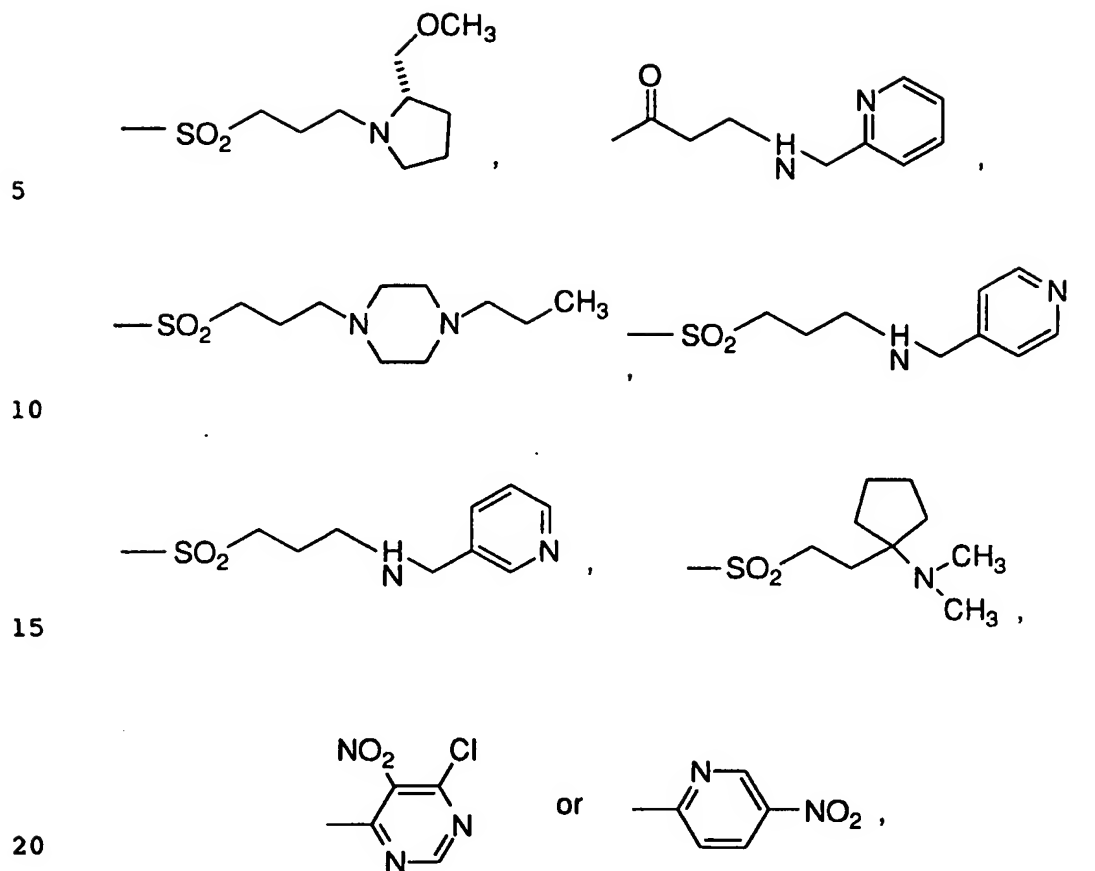
10 R¹ is -CONH₂; and

R^{11} is selected from



30

- 110 -



25. The use of the compound of Claim 1 in the preparation of a medicament for the treatment of preterm labor.

25

26. The use of the compound of Claim 1 in the preparation of a medicament for the treatment of dysmenorrhea.

27. The use of the compound of Claim 1 in the preparation of a medicament for stopping labor prior to cesarean delivery.

30

INTERNATIONAL SEARCH REPORT

International application No.

PCT/US95/03738

A. CLASSIFICATION OF SUBJECT MATTER

IPC(6) : A31K 31/495, 31/44; C07D 403/00, 401/00, 241/02, 451/00.

US CL : 514/252, 255, 278; 544/357, 359, 360, 372; 546/17.

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

U.S. : 514/252, 255, 278; 544/357, 359, 360, 372; 546/17.

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched
NONE

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

CAS ONLINE

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	J. Med. Chem., Volume 36, issued 1993, Ben E. Evans et al, "Nanomolar-Affinity, Non-Peptide Oxytocin Receptor Antagonists", pages 3993-4005.	1-19

☐ Further documents are listed in the continuation of Box C. ☐ See patent family annex.

* Special categories of cited documents:	"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
"A" document defining the general state of the art which is not considered to be of particular relevance	"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
"E" earlier document published on or after the international filing date	"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art
"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reasons (as specified)	"Z" document member of the same patent family
"O" document referring to an oral disclosure, use, exhibition or other means	
"P" document published prior to the international filing date but later than the priority date claimed	

Date of the actual completion of the international search

13 JUNE 1995

Date of mailing of the international search report

31 JUL 1995

Name and mailing address of the ISA/US
Commissioner of Patents and Trademarks
Box PCT
Washington, D.C. 20231

Facsimile No. (703) 305-3230

Authorized officer

CECILIA TSANG

Telephone No. (703) 308-1235

INTERNATIONAL SEARCH REPORT

International application No.

PCT/US95/03738

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This international report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☐ Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:
2. ☐ Claims Nos.:
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:
3. ☐ Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

Please See Extra Sheet.

1. ☐ As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.
2. ☐ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.
3. ☐ As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:
4. ☒ No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:
1-3,5,10-22,25-27(part),6-9,23 and 24

Remark on Protest .

☐

The additional search fees were accompanied by the applicant's protest.

☐

No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT

International application No.

PCT/US95/03738

BOX II. OBSERVATIONS WHERE UNITY OF INVENTION WAS LACKING

This ISA found multiple inventions as follows:

This application contains the following inventions or groups of inventions which are not so linked as to form a single inventive concept under PCT Rule 13.1. In order for all inventions to be examined, the appropriate additional examination fees must be paid.

Group I, claim(s) 1-3,5,10-22,25-27 (part), 6-9, 23 and 24, drawn to compounds wherein X is phenyl-piperazinyl, Y is -CO-(CH₂)_n-, and R is phenyl substituted with R₇ which is defined as in claim 3, composition and method of use, classified in 544/360, 514/252.

Group II, claim(s) 1-3,5,10-22,25-27(part), drawn to compounds wherein X is phenyl-piperazinyl, Y is -CO-(CH₂)_n-, and R is substituted phenyl containing no heterocyclic, composition and method of use, classified in 544/387, 388; 514/255.

Group III, claim(s) 1-3,5,10-22,25-27(part), drawn to compounds wherein X is phenyl-piperazinyl, Y is -CO-(CH₂)_n-, and R is phenyl substituted with -O-(CH₂)_n-N-(R₂)Z-R₈, compositions and method of use.

Group IV, claims 1-3,5,10-22,25-27 (part), and 4, drawn to compounds other than above, compositions and method of use.

The inventions listed as Groups I-III and IV do not relate to a single inventive concept under PCT Rule 13.1 because, under PCT Rule 13.2, they lack the same or corresponding special technical features for the following reasons:

Phenyl-piperazinyl differs significantly from spiro[1H]indene-1,4'-piperidiny. One skilled in the art would not consider them as functional equivalents of each other. Prior art which may anticipated or render obvious one of the groups would not necessarily do the same for the remaining groups.

**This Page is Inserted by IFW Indexing and Scanning
Operations and is not part of the Official Record**

BEST AVAILABLE IMAGES

Defective images within this document are accurate representations of the original documents submitted by the applicant.

Defects in the images include but are not limited to the items checked:

- ☒ **BLACK BORDERS**
- ☐ **IMAGE CUT OFF AT TOP, BOTTOM OR SIDES**
- ☐ **FADED TEXT OR DRAWING**
- ☐ **BLURRED OR ILLEGIBLE TEXT OR DRAWING**
- ☐ **SKEWED/SLANTED IMAGES**
- ☐ **COLOR OR BLACK AND WHITE PHOTOGRAPHS**
- ☐ **GRAY SCALE DOCUMENTS**
- ☐ **LINES OR MARKS ON ORIGINAL DOCUMENT**
- ☐ **REFERENCE(S) OR EXHIBIT(S) SUBMITTED ARE POOR QUALITY**
- ☐ **OTHER:** _____

IMAGES ARE BEST AVAILABLE COPY.

As rescanning these documents will not correct the image problems checked, please do not report these problems to the IFW Image Problem Mailbox.